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PATENT

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for

MEDICAL DEVICES EMPLOYING POLYMERS OF SPECIFIC CHARACTERISTICS AND THEIR USES

by

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MEDICAL DEVICES EMPLOYING POLYMERS OF SPECIFIC CHARACTERISTICS AND THEIR USES

Related Applications

This application claims priority to U.S. Provisional Application Serial No. 60/461,923, filed April 10, 2003, which is incorporated by reference herein in its entirety to the extent permitted by law.

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to medical devices comprising a polymer(s) of pre-determined characteristics that is suitable for releasing an active agent(s) under specific conditions.

Description of the Background

The safe and effective delivery of an active agent(s) to a specific location enables a site- that, in general, is associated with lesser other effects than more widespread delivery. Site-specific delivery is particularly desirable for the treatment of localized conditions in many fields, e.g. cancer; cardiovascular; orthopedic, dental, wounds, auto-immune disease such as arthritis or gastrointestinal (G.I.). Site-specific delivery permits the delivery of proteins and nucleic acids as well.

Polymers are an effective form of drug delivery, whose use began in the 1960s in the form of controlled-release oral formulations coated with non-therapeutic polymers that release the contained agent(s). The agents were admixed or appended to the polymer backbone directly or through linkers. Many formulations induce inflammation and/or host response at the site of delivery, or have low and/or unpredictable potency, breakdown products, non-zero-order release rates and burst effects or spikes of drug delivery. Existing stents, grafts, implants, and devices such as surgical and wound healing devices, among others, frequently induce or are associated with undesirable side effects such as one or more of inflammation, swelling, infection, adjacent tissue hyperproliferation, capsule, granuloma or fibroma formation ("the foreign body response" surrounding the implant), or pain.

More biocompatible polymer coatings and other surface technologies employed to coat devices employed to reduce inflammation, swelling, infection, hyperproliferation of adjacent tissues, foreign body response and/or pain, have been non-biodegradable due to the inherently highly inflammatory and unpredictable nature of the biodegradable polymers. Non-biodegradable coatings are disadvantageous, in addition, because they suffer from fatigue over time and they delaminate.

Thus, there still is a need for formulations and medical devices employing polymers that provide a range of flexibility, hardness, biocompatibility, loading capacity and duration of delivery while avoiding the above described disadvantages.

SUMMARY OF THE INVENTION

This invention relates to devices and compositions comprising a polymer(s) that release(s) an active agent(s) under specified conditions that may be employed in specific treatment methods. Formulations and medical devices in accordance with this patent may be formed of a polymer(s), or its surface(s) may comprise a polymer(s), or several layers or coatings of a polymer(s), while the core is formed of another material, e.g. an active agent(s), a polymer(s), and the like. The agent(s) may be incorporated into the polymer backbone, appended to it, or mixed with the polymer(s) in any of many forms known in the art. The agents present in the backbone and in the mixture may be the same or different, and active or activatable upon release.

Other advantages of the present invention will be readily appreciated as the same becomes better understood by reference to the following brief description of the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a continuous microencapsulation process of a polymer, protein, peptide, small molecule, water-soluble and hydrophobic drug, and drugs in a polymer where the components are added to an mechanically agitated water/surfactant mixture to form an emulsion of microdroplets, and extracted with water to remove solvent and form hardened microcapsules or microspheres for collection by centrifugation, filtration or the like.

Figure 2 shows several hollow needle-type carriers 12 for use with the invention.

Figure 3 illustrates placement of pellets, "biobullets," or seeds **10** of the invention inside the hollow cavity or chamber of a bioerodable needle-type carrier.

Figure 4 shows possible structuring of layers of coatings, in which one or more of these layers contains a polymerized drug, for implantable medical and veterinary devices. (a) Single layered coating. (b) Multiple layered coating in which the layers may have different compositions and physical properties, including thickness, and in which the top layer(s) is/are not comprising of the polymerized drug and the bottom layer(s) is/are comprised of a polymerized drug. (c) Bilayered coating in which the top and bottom layers are comprised of polymerized drugs with different compositions.

Figure 5 shows hardness of coatings of polymerized salicylic acid on stainless steel, as measured in the ASTM test for pencil hardness.

Figure 6 shows flexibility of coatings of polymerized salicylic acid on stainless steel, as measured in the ASTM test using a conical mandrel.

Figure 7 shows adhesion between coatings of polymerized salicylic acid and stainless steel, as measured in the ASTM test for adhesion.

Figure 8A shows the rate of generation of salicylic acid by the bioerosion of a coating of polymerized salicylic acid.

Figure 8B shows cumulative mass of salicylic acid generated by the bioerosion of a coating of polymerized salicylic acid.

Figure 9A shows cumulative masses in a bathing solution of PBS resulting from simultaneous generation of salicylic acid by the bioerosion of a coating of polymerized salicylic acid (PX510) and release of paclitaxel from that coating.

Figure 9B shows cumulative masses in a bathing solution of PBS resulting from simultaneous generation of salicylic acid by the bioerosion of a coating of polymerized salicylic acid (PX749) and release of paclitaxel from that coating.

Figure 10 shows glass transition temperature, tensile modulus, yield strength, and elongation at failure of polymerized salicylic acid.

Figure 11 shows cumulative masses in a bathing solution of PBS with 25% ethanol resulting from simultaneous generation of salicylic acid by the bioerosion of a coating of polymerized salicylic acid and release of sirolimus from that coating.

Figure 12 shows changes in molecular weight, hardness, flexibility, and adhesion for coatings of polymerized salicylic acid on stainless steel treated with E beam or gamma irradiation relative to similar untreated coatings.

Figure 13A shows rate of generation of salicylic acid by the bioerosion of a coating of untreated and E beam-treated polymerized salicylic acid.

Figure 13B shows cumulative mass of salicylic acid generated by the bioerosion of a coating of untreated and E beam-treated polymerized salicylic acid.

Figure 14 shows polydiflunisal anhydride polymer (PX242 20-53) and diflunisal elution in μg over time (days). Diamonds and square represent two replicates of poly-diflunisal coated coupons.

Figure 15 is a graph showing poly-diflunisal anhydride polymer (PX242 20-53) and diflunisal elution in percent diflunisal over time (days). Diamonds and square represent two replicates of poly-diflunisal coated coupons.

Figure 16 shows erosion of poly-salicylic anhydride polymer (PolyAspirin I) and of poly-diflunisal anhydride polymer (PolyAspirin II) in cumulative percent generated over time.

Figure 17 shows erosion profile for a poly-salicylic anhydride polymer (PolyAspirin I).

Figure 18 shows erosion profile for a poly-diflunisal anhydride polymer (PolyAspirin II).

Figure 19 shows effect of molecular weight on erosion of poly-diflunisal anhydride polymers (PolyAspirin II) of different molecular weights in cumulative diflunisal generated over time.

Figures 20 shows tuning mechanical properties of poly-salicylic anhydride polymer (PolyAspirin I) and of poly-diflunisal anhydride polymer (PolyAspirin II) in T_g(°C) over "Number of Carbon Atoms in Linker."

Figure 21 shows thermoanalysis of poly-salicylic anhydride polymer (PolyAspirin I) and of poly-diflunisal anhydride polymer (PolyAspirin II), including T_g, ultimate stress, ultimate elongation and toughness.

Figure 22 chart shows hardness, flexibility and adhesion properties of poly-salicylic anhydride polymer (PolyAspirin I) and of poly-diflunisal anhydride polymer (PolyAspirin II).

Figure 23 shows hardness, flexibility and adhesion properties of poly-diflunisal anhydride polymer (PolyAspirin II) and poly-diflunisal anhydride polymer admixed with paclitaxel.

Figure 24 shows erosion of poly-diflunisal anhydride polymer (PolyAspirin II) and poly-diflunisal anhydride polymer admixed with paclitaxel in cumulative percent diflunisal generated and cumulative percent paclitaxel generated over time.

Figure 25 shows erosion of untreated or sterilized poly-diflunisal anhydride polymer (PolyAspirin II) in cumulative percent generated over time.

Figure 26 shows hardness, flexibility and adhesion properties of poly-salicylic anhydride polymer (PolyAspirin I) and of poly-diflunisal anhydride polymer (PolyAspirin II) with γ irradiation.

Figure 27 shows hardness, flexibility and adhesion properties of poly-salicylic anhydride polymer (PolyAspirin I) and of poly-diflunisal anhydride polymer (PolyAspirin II) after E beam sterilization.

Figure 28 shows kinetics of NSAID generation for PolyAspirin I (I), PolyAspirin II (II), and PolyAspirin III (III).

Figure 29 shows a light microscopy photo of a 2P 315 LAD well deployed stent with concentric neointimal growth consisting of smooth muscle cell growth with proteoglycans.

Figure 30 shows a light microscopy photo of a 2P 315 LCx deployed stent; extensive malapposition of the stent struts with underlying medial necrosis can be seen; the distal sections are worse. There is moderate to severe platelet/fibrin deposition around stent struts with inflammation and hemorrhage.

Figure 31 shows a light microscopy photo of a 2P 315 RCA well deployed stent with concentric neointimal growth consisting of smooth muscle cells, collagen, and proteoglycans.

Figure 32 shows a light microscopy photo of a 2P 316 LAD stent exhibiting concentric noeintimal growth with granulomas around stent struts. Mild to moderate fibrin accumulation can be seen.

Figure 33 shows a light microscopy photo of a 2P 316 RCA poorly deployed stent with severe malapposition; medical necrosis with moderate to severe fibrin deposition with hemorrhage can be seen.

Figure 34 shows a light microscopy photo of a 2P 339 LAD stent exhibiting malapposition with minimal neointimal growth; the midsection is deployed over a branch vessel and there is necrosis with extensive fibrin and hemorrhage and giant cell reactions around the stent struts.

Figure 35 shows a light microscopy photo of a 2P 339 LCx stent that is well expanded; concentric neointimal growth of smooth muscle and proteoglycans can be seen. Stent struts show moderate to sever fibrin deposition while inflammation is minimal.

Figure 36 shows a light microscopy photo of a 2P 339 RCA stent that is well deployed and displays concentric neointimal growth consisting of smooth muscle cells and proteoglycans.

Figure 37 shows a light microscopy photo of a control bare stent harvested at 7 days; the struts are well expanded and the lumen is widely patent. The high power view on the right shows a neointima of mostly fibrin (arrow) with a few smooth muscle and inflammatory cells.

Figure 38 shows a light microscopy photo of a rabbit iliac artery stent coated with PolyAspirin I (thin coating). The struts are well expanded and the lumen is widely patent. The high power view on the right shows a neointima consisting of fibrin (arrow), some smooth cells, and proteoglycan.

Figure 39 shows a light microscopy photo of a rabbit iliac artery stent coated with a PolyAspirin I (thick coating). The struts are well expanded and the lumen is widely patent. The high power view shows a neointima consisting of fibrin, smooth muscle cells, proteoglycan and acute and chronic inflammatory cells.

Figure 40 shows a light microscopy photo of a rabbit iliac artery stent coated with PolyAspirin II. The struts are well expanded and the lumen is widely patent. A thin neointima is barely covering a stent strut and a few inflammatory cells and smooth muscle cells can be seen at the periphery of the strut.

Figure 41 shows a light microscopy photo of a control bare steel stent deployed in the rabbit iliac artery for 28 days. The struts are well expanded and the lumen is widely patent. The neointimal response is nominal and healing is near complete. The high power view shows a thickened neointima consisting mostly of smooth muscle cells and proteoglycans.

Figure 42 shows a light microscopy photo of a stainless steel stent loaded with PolyAspirin I deployed in the rabbit iliac artery for 28 days. The struts are well expanded and the lumen is widely patent. The neointimal response is nominal and healing is near complete. The high power view shows a thickened neointima consisting mostly of smooth muscle cells and proteoglycans.

Figure 43 shows a light microscopy photo of a stainless steel stent coated with PolyAspirin II deployed in the rabbit iliac artery for 28 days. The struts are well expanded and the lumen is widely patent. A collection of giant cells containing fragments of polymer grayish staining with foamy appearance and a polymer fragment is seen around a stent strut. The neointima is well healed consisting mostly of smooth muscle cells and proteoglycans.

Figure 44 (a-b) shows a scanning electron (SEM) micrograph of a polymer (PX184-55-80) coated stent according to the present invention.

Figure 45 (a-b) is a scanning electron (SEM) micrograph of a polymer (PX990-63-57) coated stent according to the present invention.

Figure 46 (a-b) is a scanning election (SEM) micrograph of a polymer (PX727-63-25) coated stent according to the present invention.

Figure 47 shows the structure of "PolyAspirin".

Figure 48 shows effects of PolyAspirin implanted into mouse palate; no foreign-body response was seen at the site receiving salicylic acid polymer 4 days post implant.

Figure 49 shows antiseptic activity of chlorhexidine, salicylic acid, diflunisal and PBS against *S. aureus*.

Figure 50 shows antiseptic activity of chlorhexidine, salicylic acid, diflunisal and vehicle against *S. epidermidis*.

Figure 51 shows PolyNSAIDs prepared from salicylic acid and diflunisal.

Figure 52 shows effect of linker chain length on PolyNSAID T_g.

Figure 53 shows effect of linker chain length on PolyNSAID hardness.

Figure 54 shows PolyNSAID hardness normalized according to intended use temperature ($T - T_g$).

Figure 55 shows adhesion load-displacement profile of polyDF on metals.

Figure 56 shows biodegradation of polySA and polyDF as 5 μm coatings on stainless steel samples.

Figure 57 shows biodegradation of polySA and polyDF as 5 μm coatings on stainless steel samples.

Figure 58 shows a pattern of salicylic acid generation during degradation indicating polySA is a bulk eroding polymer.

Figure 59 shows a pattern of diflunisal generation during degradation indicating poly DF is a surface-eroding polymer.

Figure 60 shows effect of polymer molecular weight on degradation kinetics of polyDF.

Figure 61 shows the pattern of soluble breakdown products generated during degradation of polySA.

Figure 62 shows the pattern of soluble breakdown products generated during degradation of polyDF.

Figure 63 shows simultaneous release of paclitaxel and generation of diflunisal during degradation of 20 % paclitaxel/polyDF coating on stainless steel incubated in 37 °C serum.

Figure 64 shows generation of diflunisal from polyDF-coated stainless steel samples before and after sterilization with E-beam and gamma radiation.

Figure 65 shows microspheres prepared from polyDF having a mean diameter of about 45 μm.

Figure 66 shows plasma diflunisal concentration in rats receiving a single oral dose of 25 mg diflunisal or subcutaneous injection of 250 mg polyDF microspheres (n=5).

Figure 67 shows the sequence of pathobiological response to stenting.

Figure 68 shows polyS-coated stents immediately after coating, after E-beam sterilazation, after balloon expansion, and after 2 hr in 37 °C serum.

Figure 69 shows polySA-coated stents produced no thrombosis or inflammation 7 days after implantation in rabbit iliac arteries.

Figure 70 shows polyDF-coated stents produced no thrombosis or inflammation 7 days after implantation in rabbit iliac arteries.

A more complete appreciation of the invention and other intended advantages may be readily obtained by reference to the following detailed description of embodiments of the invention and appended claims, which describe aspects of the invention and some best modes presently contemplated for carrying it out.

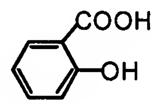
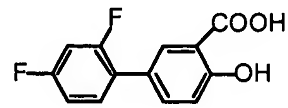
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention arose from a desire by the inventors to provide an improvement in the delivery of active agents in a manner such that avoids or minimizes detrimental effects caused by prior art technology. This invention relates to medical devices, and pharmaceutical compositions comprising a polymer(s) that release(s), under appropriate conditions, one or more agents that may be active upon delivery, or activated thereafter by means such as hydrolysis, and other cleaving processes. Polymers, compositions and devices of the invention uniquely break down into agents in amounts of extremely high potency, e.g. about 70 to about 90% agent, and in many instances even higher loads, and provide a medium for controlled or sustained delivery. These polymers and compositions may be used to form , or as coatings for, medical devices, or may be provided as nanoparticles or microparticles, e.g. spheres or other desired shapes for a range of delivery applications. These polymers and compositions may be used as carriers for other agents to be released as the polymer degrades as well.

Inflammation is the body's response to injury, and is generally associated with release of prostaglandins. Every inflammatory stimulus, whether caused by trauma, infection, antigen-antibody interactions, ischemia, heat or any other source, elicits a consistent physiological response that begins with the production and release of histamine and prostaglandins by the damaged tissue into the surrounding fluids. Prostaglandins produce fever, swelling, redness, and pain associated with inflammation, and these symptoms may be blocked by steroids and non-steroidal anti-inflammatory drugs (NSAIDs), the latter exerting their anti-inflammatory effect by inhibiting the COX-1 and COX-2 enzymes. Aspirin or acetylsalicylic acid is an NSAID that breaks down in the body to form acetic acid, which thins the blood by binding to an enzyme on blood cells, and salicylic acid, which inhibits both COX-1 and COX-2. In thew following paragraphs NSAIDs, and more particularly salicylic acid and diflunisal, will be employed to exemplify the release of agents from the polymers of the invention. The present polymers, however, may include any type of agent that is desired for delivery, and the characteristics of the polymer custom tailored for that specific application.

Disks of poly(anhydride-ester) polymers made of two parts salicylic acid and one part sebacic acid shown in Figure 1 generated salicylic acid for about five weeks when placed in solution at 37 C. When placed in a pH 10 buffer all the salicylic acid was generated within two days while in a pH 3 buffer less than 10% was released over six months, indicating that the polymer would bioerode in most body fluids and tissues in a reasonable period of time, except for the stomach. When thin membranes of this salicylic acid polymer were implanted into the palates of mice they reduced swelling and inflammation when compared to a control polymer exhibiting a classic "foreign-body response". See, Figure 2. The implanted salicylic acid polymer evidenced ostiogenic activity by producing almost 40% new, functional bone. This "osteogenic" effect reflects the ability of NSAIDs to block the production of prostaglandins, which promote bond resorption. Salicylic acid and diflunisal have similar potency as non-specific inhibitors of both COX-1 and COX-2 enzymes. These two drugs, however, have different properties related to their different degrees of water solubility and patterns of metabolic breakdown as shown in Table 1 below.

Table 1: Anti-Inflammatory Properties of Salicylic Acid and Diflunisal

	Salicylic Acid	**Diflunisal**
		
Molecular Weight	**138**	**250**
Water Solubility	**High**	**Very Low**
Plasma half-life (hours)	**2.5**	**8 to 12**
Clinical Use		
Single Oral Dose (mg)	**650**	**500**
Repeated Dosing	**650 mg (4xDay)**	**250 to 500 mg (2xDay)**
Plasma Levels* (µg/ml)	**150 to 300**	**50 to 190**
Metabolism		
No. Metabolites	**≥ 10**	**2**
Where Metabolized	**Liver, Intestine Other Tissues**	**Liver, Intestine**

***Anti-Inflammatory Effectiveness**

In general drugs that are highly water-soluble do not accumulate in tissues nearly as well as poorly water-soluble drugs, which readily cross cell membranes. Because diflunisal has poor water solubility, it may be expected to achieve higher tissue levels than those produced by salicylic or aspirin, both of which are highly water-soluble. This difference is reflected in the drugs' toxicities in animals, e.g. oral LD_{50} of diflunisal = 439 mg/kg, while salicylic acid's and aspirin's are 1300 mg/kg and 1100 mg/kg, respectively. Beyond this, the drugs have markedly different patterns of disposition in the body. After oral dosing, both salicylic acid, administered either as sodium salicylate or as aspirin, and diflunisal are well absorbed from the small intestine, with peak blood levels occurring with 1-3 hours. Salicylic acid also is well absorbed from the intact skin, especially when applied in oily liniments or ointments (the same probably applies to diflunisal, although the inventors are unaware of data in this regard). In contrast to salicylic acid, which readily penetrates the so-called "blood-brain barrier," very little diflunisal reaches the brain, so that the drug has little fever-reducing effect. Both salicylic acid and diflunisal are extensively bound to blood plasma proteins (80-90% of salicylate is bound, compared to 99% of diflunisal), which prolong their circulation time (plasma half-life) and effectiveness. After a single oral dose, 500 mg diflunisal is about as effective as 650 mg salicylic acid. Both drugs exhibit so-called "non-linear pharmacokinetics," which means that doubling of dosage produces greater than a doubling of drug levels, an effect that becomes more apparent with repeated dosing. However, because diflunisal remains much longer in the circulation (its plasma half-life is 8-12 hours, compared to 2.5 hours for salicylic acid), diflunisal is given only twice daily, and at lower doses than salicylic acid, which is given four times daily. Optimal anti-inflammatory effects are achieved with plasma salicylate concentrations of 150-300 μg/ml, and with diflunisal concentrations of 50-190 μg/ml. A major element that contributes to these potency and dosing differences is the extent of drug metabolism. Salicylic acid is extensively and rapidly metabolized by conjugation (with glucuronic acid and/or glycine) and oxidation to at least 10 different inactive metabolites, which are excreted mainly in the urine. While most salicylate metabolism occurs in the liver, it also proceeds in many other tissues throughout the body. In contrast, diflunisal is less extensively metabolized, with two soluble glucuronide conjugates accounting for almost 90% of the administered dose. Most of this metabolism occurs during absorption through the small intestine, and in the liver, but not in other tissues, and results in the therapeutic effects of diflunisal in tissues being generally stronger and longer lasting than those of salicylic acid.

Activity and Effectiveness of Polymers of the Invention

While salicylic acid and diflunisal are well known for their anti-inflammatory effects, they also have significant antiseptic potency. The anti-microbial activity of benzoic acid and its derivatives, including salicylic acid, has long been recognized. Anti-microbial activity refers to the ability to destroy, prevent the growth of, or prevent the pathogenic action of bacteria, fungi, and/or viruses.[i] The commonly used antibiotic/anti-fungal/antiviral medicines accomplish this by interfering with microbial replication or metabolism over relatively long periods of time, which creates opportunities for pathogens to "mutate around" the interference and become resistant to the medicines. While there is no concise distinction between "anti-microbial" and "antiseptic" effects, e.g. an antiseptic is defined as ". . . an agent capable of inhibiting the growth of infectious agents", antiseptic agents are generally considered to minimize the development of bacterial resistance. This distinction is demonstrated by the fact that surface-acting antiseptics, e.g. triclosan, iodine, betadine, chlorhexidine, etc., remain highly effective despite their long history of use.

The antiseptic effectiveness of salicylic acid and diflunisal compared to chlorhexidine, a commonly-used antiseptic agent. Antiseptic effectiveness was evaluated against Staphylococcus

aureus and Staphylococcus epidermidis, common bacteria that reportedly are responsible for most infections associated with implanted and percutaneous orthopedic devices. Salicylic acid and chlorhexidine were evaluated at a concentration of 2%, while the limited solubility of diflunisal allowed testing only at about 0.25%. Phosphate-buffered saline (PBS) served as a control. Antiseptic effectiveness was expressed as the logarithmic reduction of bacteria concentration at various times. Against S. aureus (Figure 3), chlorhexidine produced immediate (Day 0) antisepsis, reducing the bacterial concentration below the limit of quantitation. Salicylic acid and PBS had no immediate effect at Day 0 (i.e., after 20-40 minutes' exposure), while diflunisal was strongly effective, reducing the bacterial concentration by about 99.99% (i.e., from about 2 million CFU/ml to about 200 CFU/ml). By Day 7, all three tested agents: chlorhexidine, salicylic acid, and diflunisal had reduced the bacterial concentration below quantitation, while the bacterial concentration increased in the PBS control. These effects were maintained on Day 14 and Day 28 (not shown). A similar pattern was seen against S. epidermidis (Figure 4). Both chlorhexidine and diflunisal produced immediate antisepsis, reducing the bacterial concentration below the limit of quantitation. Salicylic acid and PBS had no immediate effect at Day 0. By Day 7, chlorhexidine, salicylic acid, and diflunisal had reduced the bacterial concentration below quantitation. These effects were maintained on Day 14 and Day 28 (not shown). Day 7 bacterial concentration decreased in the PBS control, then increased by Day 14 (this pattern is typical with S. epidermidis). USP requirements for antimicrobial effectiveness against bacteria vary depending on the type of intended application. Drugs are considered effective for "Category 1" agents (injections, emulsions and ophthalmic products made with aqueous vehicles) if they produce at least 1.0 log reduction in bacterial concentration at Day 7, at least 3.0 log reduction at Day 14, and no loss of effectiveness at Day 28. For "Category 2" products (topically used products made with aqueous vehicles, and non-sterile nasal products and emulsions), drugs are considered effective if they produce at least 2.0 log reduction in bacterial concentration at Day 14, and no loss of effectiveness at Day 28. Both salicylic acid and diflunisal clearly meet these criteria. These results are consistent with a Canadian regulatory monograph that rates salicylic acid as an effective antiseptic (antibacterial) skin cleanser at concentrations of 0.5%-3.5% (chlorhexidine is effective at 2%-4%).

The present invention also relates to pharmaceutical compositions comprising a polymer(s) that breaks down as described above to release an agent(s) under specified conditions. The polymer(s) suitable for formulations may similarly comprise an agent(s) in their backbone and/or have one or more agents appended to it or mixed in the formulation as described above.

The present invention relates to medical devices comprising a polymer(s) that are capable of breaking down to release an agent(s), either active or that may be activated in situ, for example at physiological conditions. In one embodiment, the medical device comprises a polymer comprising at least one active agent(s) or a pro-agent(s) that is(are) incorporated into the polymer backbone. In another embodiment, the polymer further comprises at least one agent(s) that is not incorporated into the polymer backbone. The agent(s) present in the backbone, appended to it, or otherwise admixed may be the same or different. The medical devices of the invention comprising at least one polymer(s) on all or a part of their surface, and may be used, for example, to deliver the agent to a pre-determined site for effecting a specified action, such as reduce or eliminate an adverse condition associated with the use of the bare device. In one embodiment, the medical device is entirely formed of a polymer(s) that break down in situ, e.g. by hydrolysis or enzymatic activity of an agent(s). The medical devices may be formed in their entirety of the polymer, or comprise layers thereof, or be coated by a polymer(s), or many other possible configurations that will permit, for example release of an agent or different agents at different rates or times. One or more polymers may be arranged in

accordance with this invention in alternating layers or coating either in the formation of the device or formulation, or by subsequent coating of a device or formulation.

The present device may be in the form of a stent, mesh, suture, pin, cuff, catheter, contraceptive device, reconstructive dental structure and tooth, orthopedic structure, drug delivery device, sensor, stitches, meshes, wound closure, implant, and the like. These devices may be formed of one or more polymers, and in addition may comprise an agent(s) mixed therein. In another embodiment, these devices may be made of another material, such as metal, and the like, and have one or more of their surfaces or a portion thereof covered with the polymer(s). The stent and other devices may comprise a polymer(s) of at least one agent(s), and the same agent(s) may also be mixed into the polymer matrix. The stent and other devices may also comprise several layers of polymer(s) in accordance with the invention, which may comprise one or more agents within the backbone, and mixed in the polymer matrix.

The devices of the invention may be employed for delivering an agent(s) to a specific site, such as is the case with the stent where the delivery may be to an interior surface of a vein or an artery. The polymers, medical devices, pharmaceutical compositions and methods of treatment provided herein may be designed to reflect advantages such as, e.g., the ability to deliver a high potency or concentration of drug by weight if desired; a near "zero-order" drug release over short or long periods if desired; ease of fabrication into coatings, fibers, microspheres, pellets, etc.; little or no evidence of a "burst effect" or initial spike of drug; predictable breakdown products; multiple routes of administration; and localized delivery for improved efficacy and reduced side-effects. Furthermore, the polymers, medical devices, pharmaceutical compositions and methods of treatment provided herein may be designed such that they do not induce an inflammatory response when administered to or implanted within a host.

An advantage of the present invention is that it may be used for controlling the onset and progression of adverse physiological conditions at the site of a medical device or method of treatment. A directed application of pharmaceutical treatment circumvents the need for a general, i.e. "whole-body" or oral, administration of the necessary therapeutics. Accordingly, such directed application of therapeutics provides faster, more targeted relief of the adverse conditions while minimizing side effects of the administration of the therapeutics. While the present invention may be embodied in many different forms, several specific embodiments are discussed herein with the understanding that the present disclosure is to be considered only as an exemplification of the principles of the invention, and it is not intended to limit the invention to the embodiments illustrated.

Definitions

The following definitions are used throughout this patent unless otherwise indicated. The article "a" and "an" as used herein refers to one or to more than one (i.e. at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element. As used herein, "active agent" refers to a substance that has a physiological effect when present in a living system. A "physiological effect" may be, for example, any effect on the functioning of an organism, such as, e.g., alteration of normal function, alteration of abnormal function, and/or restoration to normal function. A physiological effect may include, but is not limited to, binding to a biomolecule, i.e. DNA, protein, carbohydrate, lipid, etc., inhibition of enzyme activity, and sequestration of small molecule cofactors, i.e. metal ions, amino acids, etc. An active agent may be a drug or therapeutic, for example, a compound or precursor of a compound used to treat a specific disease or medical condition. As used herein, "administering an active agent near the site," means applying the agent proximal to the site, so that the agent may produce the desired or stated therapeutic

effect (e.g., reduce bone resorption at the site). Alkyl, alkoxy, etc. denote both straight and branched groups; but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. The term "amino acid," comprises the residues of the natural amino acids, e.g. Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val, in D or L form, as well as unnatural amino acids, e.g. phosphoserine, phosphothreonine, phosphotyrosine, hydroxyproline, gamma-carboxyglutamate; hippuric acid, octahydroindole-2-carboxylic acid, statine, 1,2,3,4,-tetrahydroisoquinoline-3-carboxylic acid, penicillamine, ornithine, citruline, β-methyl-alanine, para-benzoylphenylalanine, phenylglycine, propargylglycine, sarcosine, and tert-butylglycine). The term also comprises natural and unnatural amino acids bearing a conventional amino protecting group (e.g. acetyl or benzyloxycarbonyl), as well as natural and unnatural amino acids protected at the carboxy terminus, e.g. as a (C_1-C_6) alkyl, phenyl or benzyl ester or amide; or as an □- methylbenzyl amide). Other suitable amino and carboxy protecting groups are known to those skilled in the art. See for example Greene, T.W.; Wutz, P.G.M., in Protecting Groups in Organic Synthesis, Second Edition, New York, John Wiley & Sons, Inc. (1991), and references cited therein. As used herein, an agent is "appended" to a polymer when the agent is bonded to the polymer as a side chain or side group, but is not part of the polymer backbone. Preferably, the agent is bonded to the polymer through a linkage that is suitable to release the agent when the polymer is administered according to the methods of the invention. For example, the agent may conveniently be linked to a polymer through a hydrolyzable linkage such as an anhydride or ester linkage. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. As used herein, an agent or functional group is "associated" with the polymer by direct, linear (i.e., chemically bonded) integration into the polymer backbone, chemical bonding to the polymer backbone as a side chain or side group, but not as part of the polymer backbone structure, electrostatic bonding to the polymer backbone, linkage to the polymer backbone by a linking group, pendent (i.e., an offshoot of the polymer backbone, neither oligomeric nor polymeric) attachment to the polymer backbone, or bonding to one or both ends of the polymer chain. The association used will depend on the functional characteristics (e.g., number and type of reactive groups) of the functional group. A substance is said to be "biocompatible" when it has the properties of being compatible with a living system, is not toxic to the living system, and does not cause an immunological reaction in the living system. A substance is said to be "biodegradable" when it is capable of being broken down into components smaller than its original size and structure when it is present in a living system. As used herein, the term "dispersed through the polymer matrix" means that an therapeutic agent is located within the matrix of a polymer such that it may be released in a controlled fashion within the body. Preferably, the polymer matrix comprises a biodegradable polymer. As used herein, the term "dissociate" indicates that a substance is broken into smaller parts. The smaller, dissociated parts of the original undissociated whole may be chemically identical to the undissociated whole or they may be chemically dissimilar to the undissociated whole. Chemical dissimilar dissociation products may be heterogeneous or homogeneous with respect to either or both of chemical properties and size. Dissociation products may also have the property of being able to recombine and create the original undissociated whole, or they may be permanently dissociated. Dissociation may occur spontaneously, as an inherent property of the undissociated whole, or dissociation may occur as a result of a physical or chemical process, such as hydrolysis of the undissociated whole. The term ester linkage means -OC(=O)- or -C(=O)O-; the term thioester linkage means -SC(=O)- or -C(=O)S-; and the term amide linkage means - N(R)C(=O)- or -C(=O)N(R)-, wherein each R is a suitable organic radical, such as, for example, hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl$(C_1. C_6)$alkyl, aryl,

heteroaryl, aryl(C_1-C_6)alkyl, or heteroaryl(C_1-C_6)alkyl. The term urethane or carbamate linkage means -OC(=O)N(R)- or -N(R)C(=O)O-, wherein each R is a suitable organic radical, such as, for example, hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, aryl, heteroaryl, aryl(C_1-C_6)alkyl, or heteroaryl(C_1-C_6)alkyl, and the term carbonate linkage means -OC(=O)O-.

The term "formed into" includes within its meaning that a polymer, compound and/or composition of the invention may be physically configured into various shapes, geometries, structures and configurations including, but not limited to, a film, fiber, rod, coil, corkscrew, hook, cone, pellet, tablet, tube (smooth or fluted), disc, membrane, microparticle, nanoparticle, "biobullet" (i.e., bullet shaped), seed (i.e., bullet shaped or targeted seeds), etc. A "functional group" as used in the present invention is a chemical moiety that may be incorporated into a polymer, e.g., into an ester, thioester, urethane, carbamate, carbonate or amide linkage of a polymer (as discussed in detail below), such that, upon hydrolysis of the polymer or by enzymatic action (for example, by action of one or more esterases) on the polymer, the therapeutic agent is obtained. These groups may independently be a hydroxy group (-OH), a mercapto group (-SH) or (-SR), an amine group (-NH-R), or a carboxylic acid (-COOH). Halo is fluoro, chloro, bromo, or iodo. As used herein, the term "healing" means the repair of a defect or non-normal condition or state. Healing may be the restoration to normal health or the process of a return to health. Heteroaryl encompasses a radical attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(X) wherein X is absent or is H, O, (C_1-C_6) alkyl, phenyl or benzyl, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto. As used herein, the term "hard tissue" includes tissue that has become mineralized, such as, for example, bone, cartilage, or both. The term "host" includes animals and plants, such as, e.g., a mammal, including a human. A host may also be a "patient". For purposes of the present invention, by "low molecular weight drug" it is meant to include any compound with one carboxylic acid group and at least one amine, thiol, alcohol or phenol group within its structure, wherein the compound has a demonstrated pharmacological activity and a molecular weight of approximately 1000 daltons or less. A "medical device" is a therapeutic device, such as, e.g., a "medical implant," that is used specifically for a medically related purpose. For example, a bone screw is both a medical device and a medical implant. The term "peptide" describes a sequence of 2 to 35 amino acids, e.g. as defined above, or peptidyl residues. The sequence may be linear or cyclic. For example, a cyclic peptide may be prepared or may result from the formation of disulfide bridges between two cysteine residues in a sequence. Preferably a peptide comprises 3 to 20, or 5 to 15 amino acids. Peptide derivatives may be prepared as disclosed in U.S. Patent Numbers 4,612,302; 4,853,371; and 4,684,620, or as described in the Examples herein below. Peptide sequences specifically recited herein are written with the amino terminus on the left and the carboxy terminus on the right. As used herein, "physiological conditions" are the conditions in a physiological system or environment, such as, e.g., within a mammal, such as a human. The physiological conditions may be "normal physiological conditions" such as conditions found in a normal, healthy patient, or "abnormal physiological conditions" such as conditions found in an unhealthy, sick, or injured patient. Physiological conditions may be found, for example, inside a mammal, or on the surface of a mammal, such as, e.g., on the mammal's skin or hair. As used in the present invention, a "sleeve" is a physical conformation of a substance in which the substance sits adjacent to and fits around the outside of a separate substance, such as, e.g., a medical or therapeutic device. For example, a plastic coating surrounding a metal rod may be considered to be a sleeve around that metal rod. For the purpose of the present invention, a sleeve may also sit adjacent to a

separate substance without completely enclosing the outer surface of the separate substance. In the present invention, a sleeve may be used to describe a substance that is formed into, for example, a coating, a film, a sheath, a wrap, a tube, a cuff, or a formed gel partially or wholly surrounding separate substance, such as, for example, a medical device. As used herein, a substance is said to be solid when it has three dimensions and has the properties of a solid, i.e., it is not a liquid or gas. For example, a piece of paper, a metal rod, and steel needle are all considered solids. As used herein, a substance is a "semi-solid" when it has properties of a solid, but also has some of the properties of a liquid, i.e., it is easily deformable by physical or chemical action. For example, gel and clay are semi-solids according to the use of the term in the present invention.

A "therapeutic agent" is an "active agent" which aids in the prevention or treatment of an undesired occurrence or condition in a living system. A "therapeutic device" is defined herein as any device that aids in the prevention or treatment of an undesired occurrence or condition in a living system. A therapeutic device that is either temporarily or permanently placed either partially or wholly inside a living system may also be referred to as a "therapeutic implant." As used herein, a functional therapeutic device may be made of more than one therapeutic device. As used herein, administering an agent "to or near the tissue" means administering the agent so that it is in direct contact with the tissue or administering the agent to a location proximal to tissue, so that the agent may produce the desired or stated therapeutic effect. A "veterinary device" is a therapeutic device that is used specifically for a medically related purpose in an animal.

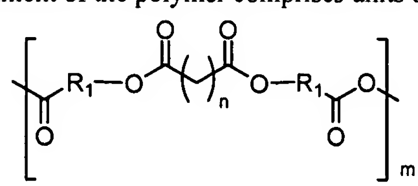
Polymers

A polymer of the invention may be any polymer suitable for delivering an active agent to the patient, such as, for example, a biocompatible and biodegradable polymer that is capable of releasing at least one active agent upon degradation and/or hydrolysis of the polymer under physiological conditions. Suitable polymers include, for example, polymers that have a polymeric backbone linking an active agent or agents into polymeric drug delivery systems. Such polymers uniquely incorporate the active agent or agents as a repeating structural component of the polymer backbone, which is developed using hydrolyzable bonds such as esters, thioesters, amides, urethanes, carbamates and carbonates as opposed to radical or aliphatic bonds. Once placed in the body of a host, such as, e.g., a mammal, such as, e.g., a human, the polymer breaks down over time and the active agent is released. In one embodiment, a suitable polymer degrades over a controlled period of time to produce relatively high, localized levels of the active agent or agents, allowing for enhanced therapeutic effects while minimizing side effects compared to the systemic delivery of drugs. In one embodiment, a suitable polymer is biocompatible, biodegradable, and demonstrates favorable solubility and processability, as well as degradation properties suitable for the desired use. In one embodiment of the invention, the active agent is released over time as the polymer hydrolyzes under physiological conditions, providing for an extended-release formulation that provides a consistent source of the therapeutic substance for an extended period of time. Suitable polymers for use in the present invention include, for example, polyesters, such as, e.g., poly(ester-esters) and poly(ester-carbonates); polyamides; and polyanhydrides, such as poly(anhydride-esters) and poly(azo-anhydrides), and are described in, e.g., e.g., U.S. Patent Nos. 6,328,988; 6,365,146; 6,468,519; 6,486,214; 6,497,895; 6,602,915; 6,613,807; 4,916,204; and 4,868,265; U.S. Published Patent Applications 2002/0071822 A1; 2002/0106345 A1; 2003/0035787 A1; 2003/0059469 A1; 2003/0104614 A1; 2003/0170202 A1; U.S.SNs 09/508,217; 10/368,288; 10/622,072; 10/646,336; 10/647,701; and International Patent Applns. WO 99/12990; WO 01/28492; WO 01/41753; WO 01/58502; WO 02/09767; WO 02/09768; WO 02/09769; WO 03/005959; WO 03/046034; WO 03/065928; and WO 03/072020; and Erdmann, L., Uhrich, K.E.,

Biomaterials, 21: 1941-1946 (2000), incorporated herein by reference. The polymer of the invention may be a polyanhydride. Preferably, the polyanhydride backbone has one or more groups that will provide an active compound upon hydrolysis or enzymatic degradation of the polymer.

In one embodiment, the polymer comprises one or more units of the chemical formula (I) R_1-A-L-A-R_1- (I), wherein R_1 independently from one another comprises one or more residues comprising an agent(s) that is released upon hydrolysis or enzymatic degradation of the polymer, A comprises independently a functional group such as an amide, thioamide, ester, thioester, carbonate, or thiocarbonate, among other labile functional groups, and L comprises one or more units of linking residue(s). . Such polymer is particularly useful for the administration of a combination of more than one agent. The polyanhydride of chemical formula (I) serves as the backbone of a polymeric drug delivery systems comprising these linked agent(s). Such polymeric drug delivery systems provide an effective means to deliver drugs in a controlled fashion to any site of a host, such as an animal or a plant. In one embodiment, the polyanhydride of chemical formula (I) links low molecular weight drug(s) with functional groups such as carboxylic acid, amine, thiol, alcohol or phenol, among many that form labile bonds, such as those having heteroatoms e.g. P, S, N, and the like. In another embodiment the polymer comprises a polyanhydride having a unit(s) comprising the chemical formula (I), wherein each R_1 and A, independently from one another, comprises and is capable of releasing aromatic agent(s), such as NSAIDs, e.g. salicylic acid or a salicylic acid derivative, or any other agent to be delivered by the polymer. Examples of suitable salicylates include, but are not limited to, diflunisal, diflucan, thymotic acid, 4,4-sulfinyldinailine, 4-sulfanilamidosalicylic acid, sulfanilic acid, sulfanilylbenzylamine, sulfaloxic acid, succisulfone, salicylsulfuric acid, salsallate, salicylic alcohol, salicylic acid, orthocaine, mesalamine, gentisic acid, enfenamic acid, cresotic acid, aminosalicylic acid, aminophenylacetic acid, acetylsalicylic acid, and the like. The identification of R and X moieties that provide aromatic polyanhydrides that hydrolyze to form such therapeutically useful salicylates may be readily determined by those of ordinary skill in the art without undue experimentation. In one embodiment, the active agent is salicylic acid.

Another embodiment of the polymer comprises units of the chemical formula (II)



(II)

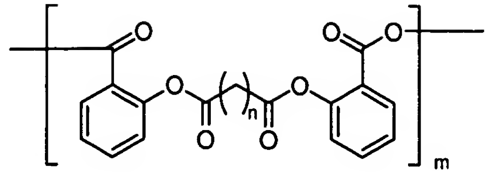
wherein n, independently from one another, comprises a linear or branched, cyclic and/or substituted carbon linker L chain, of any suitable number of carbon atoms, such as C3, C6, C8, C10, C14, C18 to C20, C24, C28, C30, and m is correlated to the overall molecular weight of the polymer. Although any agent may be polymerized in this fashion, particularly suited are aliphatic, alicyclic, aromatic small and large organic molecules that may have at least two functional groups, but could have additional groups such as OH, SH, COOH, COOR, OCOOH, OCOOR, phosphate, amine, amide, thioester, thiamide, S, P, N, halogen, ether, aldehyde, ketone, and many others that have known property regulation such as hydrophilicity, solubility, and the like. In one embodiment, the active agent is salicylic acid, and the linker is a dicarboxylic acid hydrocarbon chain with an even number of carbon atoms. The nature of the linking group L in a polymer of the invention is not critical provided the polymer of the invention possesses acceptable mechanical properties and release kinetics for the selected therapeutic application. The linking group L typically comprises a divalent organic residue having a molecular weight of from about 25, 40, 60, 100 daltons to about 140, 170, 250, 370, 400 daltons, and preferably about 40 daltons to about 200 daltons. The linking group L typically has a

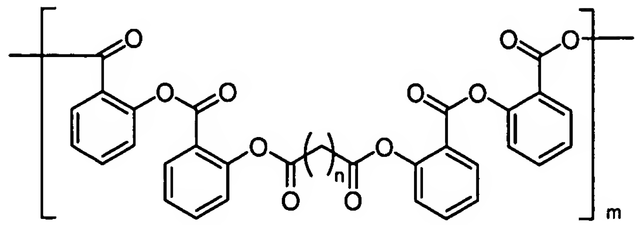
length of from about 5, 10 angstroms to about 50, 100 angstroms using standard bond lengths and angles. The linking group may be biologically inactive, or may itself possess biological activity. The linking group may also comprise other functional groups (including hydroxy groups, mercapto groups, amine groups, carboxylic acids, as well as others) that may be used to modify the properties of the polymer (e.g. for branching, for cross linking, for appending other molecules (e.g. another biologically active compound) to the polymer, for changing the solubility of the polymer, or for effecting the biodistribution of the polymer). The linking group may incorporate other hydrolytically biodegradable groups such as alpha-ester (lactate, glycolate), e-caprolactone, ortho-ester, or enzymatically biodegradable groups such as amino acids. It may be a water-soluble, non-biodegradable segment such as a polyethylene glycol, polyvinyl alcohol or polyvinyl pyrrolidone. The linking group may be a water-insoluble, non-biodegradable segment such as polypropylene glycol, polyetherurethane, or poly(n-alkyl ether). It may be an amorphous or semicrystalline biodegradable polymer, such as poly (d, l-lactide), poly (trimethylene carbonate), poly(dioxanone), polyanhydride poly(orthoester) poly(glycolide), poly(l-lactide) poly(e-caprolactone) and copolymers of e-caprolactone, glycolide, trimethylene carbonate, dioxanone, d,l-lactide, l-lactide and d-lactide. The linking group may have surfactant properties, such as a Pluronic block copolymer with polyethylene glycol and polypropylene glycol blocks. It may have polar or charged moieties, including carboxylic acid groups from poly(acrylic acid) and poly(alginates), sulfonic acid groups from poly(2-acrylamido-2-methyl-propanesulfonicacid) (AMPS), hydroxy groups from poly(vinyl alcohol), polysaccharides and poly(alginates), and amino groups from poly(L-lysine), poly(2, 2-dimethylaminoethyl methacrylate) and poly(amino acids). The linking group may be a segment that undergoes thermoreversible gellation, such as Pluronic F127 and poly (N-isopropyl acrylamide). It may incorporate structurally-reinforcing segments, such as polyetherurethane, polyesterurethane, etc. The linking group may be a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 25 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (--O--) or (--NR--), and wherein the chain is optionally substituted on carbon with one or more, e.g. 1, 2, 3, or 4, substituents selected from the group consisting of (C1-C6) alkoxy, (C3-C6) cycloalkyl, (C1-C6) alkanoyl, (C1-C6) alkanoyloxy, (C1-C6) alkoxycarbonyl, (C1-C6) alkylthio, azido, cyano,nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy. The linking group may be a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 25 carbon atoms, wherein the chain is optionally substituted on carbon with one or more, e.g. 1, 2, 3, or 4, substituents selected from the group consisting of (C1-C6) alkoxy, (C3-C6) cycloalkyl, (C1-C6) alkanoyl, (C1-C6) alkanoyloxy, (C1-C6) alkoxycarbonyl, (C1-C6) alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy. The linking group may be a peptide or an amino acid. The linking group may be a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from about 1, 3, 5, 10 to about 12, 15, 18, 18, 22, 25 carbon atoms, wherein one or more, e.g. 1, 2, 3, or 4, of the carbon atoms is optionally replaced by -O- or -NR-; or a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from about 3, 6, 9 to about 12, 15 carbon atoms, wherein one or more, e.g. 1, 2, 3, or 4, of the carbon atoms is optionally replaced by -O- or -NR- or –S-, and wherein the chain is optionally substituted on carbon with one or more, e. g. 1, 2, 3, or 4, substituents selected from the group consisting of (C1-C6) alkoxy, (C3-C6) cycloalkyl, (C1-C6) alkanoyl, (C1-C6) alkanoyloxy, (C1-C6) alkoxycarbonyl, (C1-C6) alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy. The linking group may be a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally

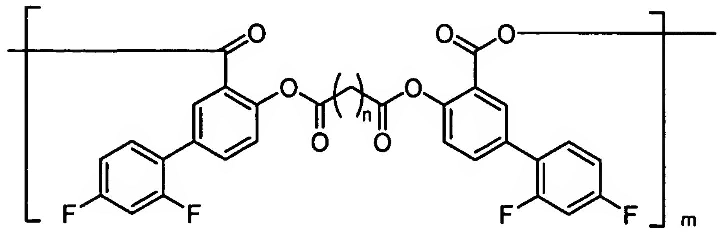
replaced by (--O--) or (--NR-); or a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms; or a divalent, branched or unbranched, hydrocarbon chain, having from 3 to 15 carbon atoms; or a divalent, branched or unbranched, hydrocarbon chain, having from 6 to 10 carbon atoms; or a divalent hydrocarbon chain having 7, 8, or 9 carbon atoms; or a divalent hydrocarbon chain having 8 carbon atoms. The index m, independently from one another, may be any suitable number of units, including, e.g. a number of units that result in a polymer with a molecular weight of about 1,500; 3,000; 5,000; 7,500; 10,000; 20,000 to about 50,000, 75,000; 100,000 dalton. The polymer(s) of this patent release their agent(s) when placed at a pH of about 3, 4, 5, 6, 7 to about 8, 9, 10, 11, 12, 13, and higher over a period of time of about one, 2, 3, 5, 10 20, 50, 75 days to about 2, 3, 5, 7, 9, 12, 24 months, or longer. When at a pH below their pKa they degrade slowly, for example 6 months or longer.

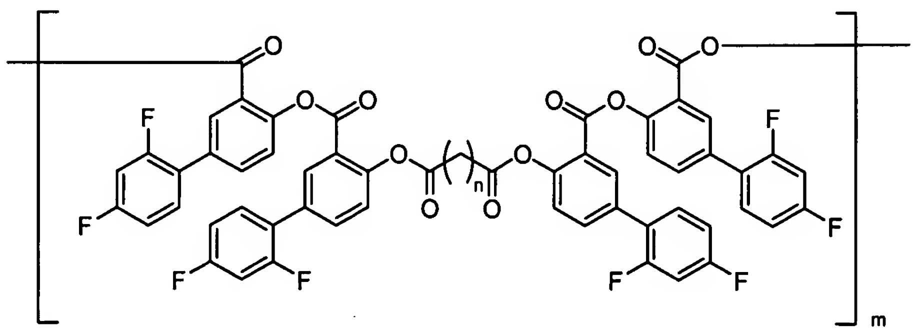
Some polymer(s) of the invention may reach an average molecular weight (MW) about 1,500; 5,000; 20,000; 50,000; 100,000; 200,000; 400,000 daltons to about 500,000; 700,000; 850,000; 1,000,000 daltons, and in some instances even higher. The agents present within the polymer structure may have groups such as carboxylic acid, amine, amide, thiol, alcohol or phenol group. Thus, when R comprises a residue of a drug as the agent, the polymer may function as a drug(s) delivery system that provides an effective amount of the agent in a controlled fashion as a function of polymer degradation at any predetermined site of a host. Polyanhydride materials have been extensively studied. See, for example, U.S. Patents 4,757,128; 4,997,904; 4,888,176; 4,857,311; 5,264,540; International Publications WO 99/12990; WO 02/09769; WO 02/09767. The inventors have discovered that anhydride polymers having high average molecular weights possess unexpected and advantageous properties that polymers having lower average molecular weights do not possess. For example, higher molecular weight polyanhydrides typically have greater mechanical strength and higher stability. Further, higher molecular weight polyanhydrides may be made into harder and thicker coatings. In one most preferred embodiment, the polymer of the invention may have an average molecular weight (MWave) of at least about 200,000, and preferably above about 250,000.

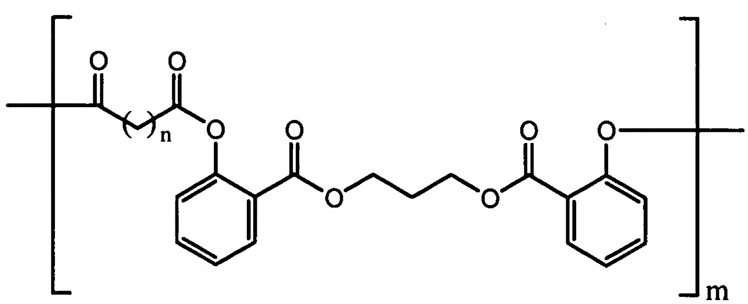
Examples of the compounds in the invention are show below.

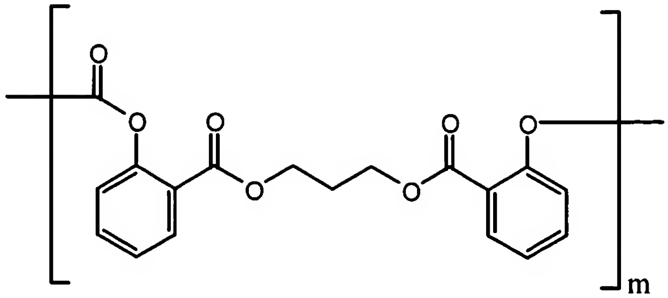




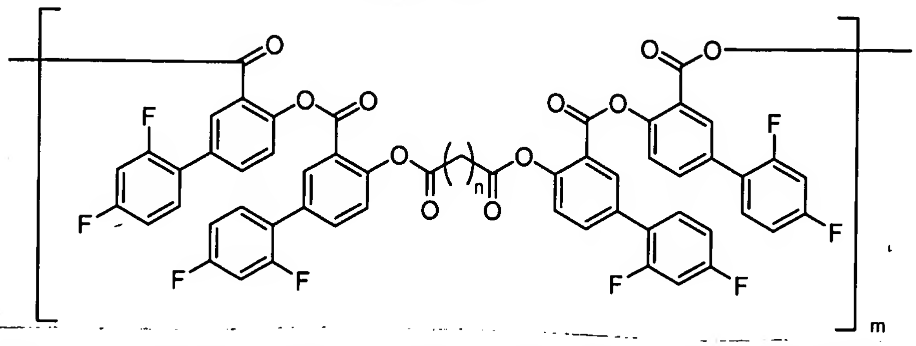








In one embodiment, the polymer comprises units of the chemical structure shown in Figure II, wherein the polymer breaks down relatively quickly, e.g. over a period of days, into the agent(s), e.g. salicylic acid, as demonstrated in Figure 28. In one embodiment, the active agent is diflunisal. The polymer may comprise units of the chemical formula (III):



(III)

wherein n may be any suitable number of carbon atoms, such as, for example, an even number of carbon atoms. In one embodiment, the active agent is diflunisal, and L is a dicarboxylic acid hydrocarbon chain with an even number of carbon atoms. A suitable even number of carbon atoms includes any even number of carbon atoms that will result in a functional polymer, e.g., about 2 to about 20 carbon atoms, about 2 to about 18 carbon atoms, about 4 to about 16 carbon atoms, about 4 to about 14 carbon atoms, about 6 to 16 carbon atoms, about 8 to 12 carbon atoms, or about 6 to about 10 carbon atoms. Further, the nature of the linking group L in a polymer of the invention is not critical provided the polymer of the invention possesses acceptable mechanical properties and release kinetics for the selected therapeutic application. The linking group L is typically a divalent organic radical having a molecular weight of from about 25 daltons to about 400 daltons. More preferably, L has a molecular weight of from about 40 daltons to about 200 daltons. The linking group L typically has a length of from about 5 angstroms to about 100 angstroms using standard bond lengths and angles. More preferably, the linking group L has a length of from about 10 angstroms to about 50 angstroms. The linking group may be biologically inactive, or may itself possess biological activity. The linking group may also comprise other functional groups (including hydroxy groups, mercapto groups, amine groups, carboxylic acids, as well as others) that may be used to modify the properties of the polymer (e.g. for branching, for cross linking, for appending other molecules (e.g. another biologically active compound) to the polymer, for changing the solubility of the polymer, or for effecting the biodistribution of the polymer). The linking group may incorporate other hydrolytically biodegradable groups such as alpha-ester (lactate, glycolate), e-caprolactone, ortho-ester, or enzymatically biodegradable groups such as amino acids. It may be a water-soluble, non-biodegradable segment such as a polyethylene glycol, polyvinyl alcohol or polyvinyl pyrrolidone. The linking group may be a water-insoluble, non-biodegradable segment such as polypropylene

glycol, polyetherurethane, or poly (n-alkyl ether). It may be an amorphous or semicrystalline biodegradable polymer, such as poly (d,l-lactide), poly (trimethylene carbonate), poly (dioxanone), polyanhydride poly (orthoester) poly (glycolide), poly (l-lactide) poly (e-caprolactone) and copolymers of e-caprolactone, glycolide, trimethylene carbonate, dioxanone, d,l-lactide, l-lactide and d-lactide. The linking group may have surfactant properties, such as a Pluronic block copolymer with polyethylene glycol and polypropylene glycol blocks. It may have polar or charged moieties, including carboxylic acid groups from poly (acrylic acid) and poly (alginates), sulfonic acid groups from poly (2-acrylamido-2-methyl-propanesulfonic acid) (AMPS), hydroxy groups from poly(vinyl alcohol), polysaccharides and poly(alginates), and amino groups from poly(L-lysine), poly(2, 2-dimethylaminoethyl methacrylate) and poly(amino acids). The linking group may be a segment that undergoes thermoreversible gellation, such as Pluronic F127 and poly(N-isopropyl acrylamide). It may incorporate structurally-reinforcing segments, such as polyetherurethane, polyesterurethane, etc. The linking group may be a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 25 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (--O--) or (--NR--), and wherein the chain is optionally substituted on carbon with one or more, e.g. 1, 2, 3, or 4, substituents selected from the group consisting of (C1-C6)alkoxy, (C3-C6)cycloalkyl, (C1-C6)alkanoyl, (C1-C6)alkanoyloxy, (C1-C6)alkoxycarbonyl, (C1-C6)alkylthio, azido, cyano,nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy. The linking group may be a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 25 carbon atoms, wherein the chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from the group consisting of (C1-C6)alkoxy, (C3-C6)cycloalkyl, (C1-C6)alkanoyl, (C1-C6)alkanoyloxy, (C1-C6)alkoxycarbonyl, (C1-C6)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy. The linking group may be a peptide or an amino acid. The linking group may be a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 25 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (--O--) or (--NR-); or a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (--O--) or (--NR--), and wherein the chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from the group consisting of (C1-C6)alkoxy, (C3-C6)cycloalkyl, (C1-C6)alkanoyl, (C1-C6)alkanoyloxy, (C1-C6)alkoxycarbonyl, (C1-C6)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy. The linking group may be a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (--O--) or (--NR-); or a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms; or a divalent, branched or unbranched, hydrocarbon chain, having from 3 to 15 carbon atoms; or a divalent, branched or unbranched, hydrocarbon chain, having from 6 to 10 carbon atoms; or a divalent hydrocarbon chain having 7, 8, or 9 carbon atoms; or a divalent hydrocarbon chain having 8 carbon atoms. The variable m may be any suitable number of repeating units, including, e.g. a number of repeating units that results in a polymer with a molecular weight of about 1,500 daltons to about 1,000,000 daltons; about 1500 daltons to about 85,000 daltons, about 1500 daltons to about 75,000 daltons, about 1500 daltons to about 60,000 daltons, about 1500 daltons to about 50,000 daltons, about 1500 daltons to about 35,000 daltons, about 1500 daltons to about 20,000 daltons, about 1500 daltons to about 15,000 daltons, or about 1500 daltons to about 10,000 daltons, calculated by Gel Permeation Chromatography (GPC) relative to narrow molecular weight polystyrene

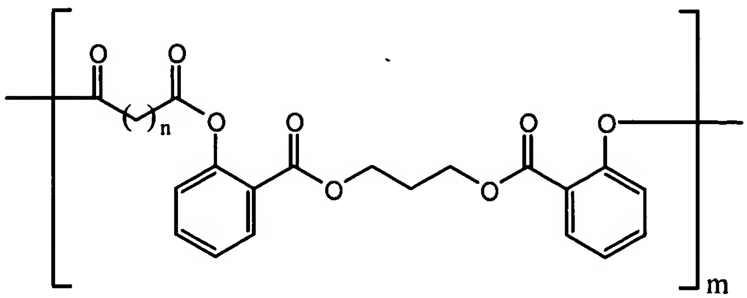
standards. Further, the polymers of the invention may have an average molecular weight of about 1500 daltons to about 1,000,000 daltons. The compounds that form the R group contained within the polymer structure may have one carboxylic acid group and at least one amine, thiol, alcohol or phenol group. Thus, when R is the residue of a therapeutic agent (drug), these polymers may function as drug delivery systems, which provide an effective means to deliver drugs in a controlled fashion as a function of polymer degradation to any site of a host.

Suitable monomers are polymerized to provide the polyazo compounds. In one embodiment, the polymer comprises one or more units of the chemical formula $-A-R^1-N=N-R^1-(A-L)_n-$ (III), and/or units of the chemical frormula $-(A-R^1-N=N-R^1-(A-L)_n)_x-$ (IV), wherein each R^1-N is a group that will provide a biologically active compound upon hydrolysis of the polymer; each A comprises anhydride, amide, thioamide, thioester, or ester; and L is a linking group; where n is 0 or 1 and x represents the number of repeating groups (e.g. x may be an integer from 2 to about 100, preferably from 2 to about 50, and more preferably, from 5 to 50). Suitable monomers are polymerized to provide the polyazo compounds. In one embodiment, the polyazo compound is a compound containing at least one free amine group to form the azo group and at least one free carboxylic acid group, alcohol group or amine group available for reactions which may self- polymerize or co-polymerize with carboxylic acid groups or bis(acyl) chlorides. In one embodiment, the polymer comprises an active agent incorporated in a poly(azo-anhydride). In one embodiment, the polymer comprises a polymeric drug delivery system for oral delivery of a drug comprising a poly(azo-anhydride) where the drug is 5-ASA or 4-ASA. The polymer may have two, three, or more different R groups that will each provide a different active agent upon hydrolysis of the polymer. Such polymers are particularly useful for the administration of a combination of two or more active agents to a host, such as an animal or plant.

In yet another embodiment, the polyazo compound is a compound containing at least one free amine group to form the azo group and at least one free carboxylic acid group, alcohol group or amine group available for reactions which may self- polymerize or co-polymerize with carboxylic acid groups or bis(acyl) chlorides. In one embodiment, the polymer comprises an active agent incorporated in a poly(azo-anhydride). In one embodiment, the polymer comprises a polymeric drug delivery system for oral delivery of a drug comprising a poly(azo-anhydride) where the drug is 5-ASA or 4-ASA. The polymer may have two, three, or more different R groups that will each provide a different active agent upon hydrolysis of the polymer. Such polymers are particularly useful for the administration of a combination of two or more active agents to a host, such as an animal or plant. The polymer may be a homopolymer, or a co-polymer. The polymer of the invention typically have a glass transition temperature (Tg) about –10, -5, 0, 10, 30, 50 to about 60, 70, 80, 100, 130, 160, 200 C. One preferred group of polymers is that where the glass transition temperature Tg is in the vicinity of about 50 C. The polymer may comprise any number of agents, whether biologically, diagnostically, therapeutically active or inactive, or whether they have other activities that make them suitable for applications other than to microorganisms, plants, animas or humans. In fact any type of agent that may be polymerized or mixed, dispersed or otherwise incorporated into a polymeric formulation, and released from its large molecular weight structure is suitable for use in this application. Such agent(s) may be loaded in amounts of about 0, 5, 10, 15, 20 %w/w to about 25, 30, 35, 40, 45, 50 %w/w, although other amounts are also contemplated. In one preferred embodiment, the polymer comprises a non-steroidal anti-inflammatory agent (NSAID), such as, e.g., salicylic acid and/or diflunisal. Such polymers include for example, polymers comprising repeating units of Formula I, III, and/or Formula IV. NSAIDs are thought to block the fever, swelling, redness and pain associated with inflammation. In one embodiment, the polymer is combined with one or more agents in any suitable manner, such as, e.g. by physically admixing, embedding, appending, or dispersing the

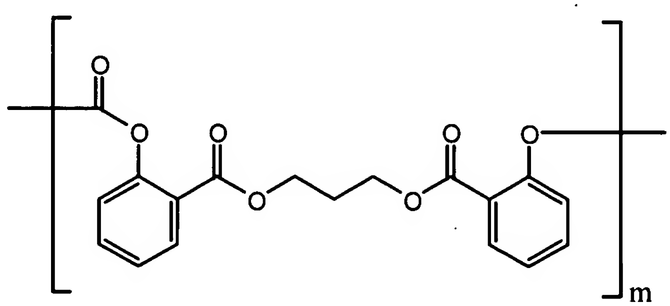
active agent in the polymer matrix. The agent(s) may be added to the backbone, chemically linked in the backbone through a linker or spacer molecule, directly or indirectly chemically linked to a chemical group attached to the backbone of the polymer and/or electrostatically, or in any other manner attached to the polymer or the polymer backbone. In one embodiment, the active agents may be attached to repeating units of the polymers of the present invention by covalent bonds linked to an Ar ring or an R organic moiety, providing for sustained release of the agent, e.g. an active agent, or it may merely reside in the unoccupied spaces present in the polymer. In another embodiment, the active agent forms a salt with the polymer or the polymer backbone. In one embodiment, the agent is located in the unoccupied spaces of a polymer and is present as a homogeneous functional group or it may be incorporated into a salt, micelle, liposome, or heterogeneous aggregate. The polymer may comprise a polymer backbone that comprises one or more similar or different residues comprising an agent(s) that will be released either directly or indirectly, for instance by hydrolysis or enzymatic degradation of the polymer. In addition, the polymer may also comprise a second or additional agent that is physically admixed, embedded or dispersed in, or combined with the polymer as is known in the art. In one embodiment, the polymer comprises units of the chemical structure of Formula (III), where the agent comprises an NSAID, and also comprises an NSAID physically admixed, embedded or dispersed in the polymer matrix.

In one embodiment, the polymer comprises units having the chemical formula of figure III, wherein the polymer breaks down into diflunisal over a period of weeks as demonstrated in Figure 28. The polymer may be a polyester or a polyamide. In one embodiment, the polymer is comprised of compounds containing at least two free alcohol or phenol groups or at least two free amine groups available for reactions which co-polymerize with carboxylic acid groups or bis(acyl) chlorides. For example, a polymer of the invention may comprise one or more units of chemical formula $-R_1-A-L-A-$ (IV), wherein R_1 is group that will provide a active compound upon hydrolysis or enzymatic degradation of the polymer; each A is independently an amide linkage, a thioester linkage, or an ester linkage; and L is a linking group. A polymer of the invention may also be a polymer that comprises one or more units of chemical formula $-R_2-A-L-A-R_3-A-L-A-$ (V), wherein R_2 and R_3 are each independently a group that will yield a active compound upon hydrolysis or enzymatic degradation of the polymer; each A is independently an amide, thioester, or ester linkage; and each L is independently a linking group. Such a polymer, wherein R_2 and R_3 are groups that will yield differing active compounds upon hydrolysis or enzymatic degradation of the polymer, are particularly useful for the administration of a combination of two therapeutic agents to an animal. Another exemplary polymer of the invention is a co-polymer that comprises one or more units of chemical formula $-R-A-L_2-A-R-A-L_3-A-$ (VI), wherein L_2 and L_3 are each independently a linking group; each A is independently an amide, thioester, or ester linkage; and each R is independently a group that will yield a active compound upon hydrolysis or enzymatic degradation of the polymer. Such a polymer, wherein L_2 and L_3 are linking groups that impart different physical properties to the polymer, are particularly useful for customizing the physical characteristics of the polymer for a specific application. In one embodiment, the active agent is salicylic acid. In one embodiment, the polymer is a poly(ester-ester). In another embodiment the polymer comprises units having the chemical formula (VII)



(VII)

wherein n may be any suitable number of carbon atoms, such as, for example, an even number of carbon atoms. A suitable even number of carbon atoms includes any even number of carbon atoms that will result in a functional polymer, e.g., about 2 to about 20 carbon atoms, about 2 to about 18 carbon atoms, about 4 to about 16 carbon atoms, about 4 to about 14 carbon atoms, about 6 to 16 carbon atoms, about 8 to 12 carbon atoms, or about 6 to about 10 carbon atoms. Further, the nature of the linking group L in a polymer of the invention is not critical provided the polymer of the invention possesses acceptable mechanical properties and release kinetics for the selected therapeutic application. The linking group L is typically a divalent organic radical having a molecular weight of from about 5, 10, 15, 20, 25, 40 to about 100, 200, 300, 400 Dalton, and a length of from about 5, 10, 30, 40 to about 50, 75, 100 Angstrom using standard bond lengths and angles. The linking group may be biologically inactive, or may itself possess biological or other activity. Other characteristics of the linking group were described above. The polymer may comprises units having the chemical structure of Figure VII, and the polymer breaks down over a period of months into salicylic acid as demonstrated in Figure 28. Another exemplary polymer of the invention is a co-polymer that comprises one or more units of chemical formula -R-A-L-A-R-A- (IX), wherein L is a linking group; each A is independently an amide, thioester, carbonate, carbamate, urethane or ester linkage; and each R is independently a group that will yield a active compound upon hydrolysis or enzymatic degradation of the polymer. In one preferred embodiment, the active agent comprises an NSAID(s), preferably salicylic acid and/or diflunisal. In another embodiment the polymer comprises poly(ester-carbonate) bonds. One preferred polymer comprises units of the chemical formula



(X)

wherein n may be any suitable number of carbon atoms, such as, for example, an even number of carbon atoms. A suitable even number of carbon atoms includes any even number of carbon atoms that will result in a functional polymer, e.g., about 2 to about 20 carbon atoms, about 2 to about 18 carbon atoms, about 4 to about 16 carbon atoms, about 4 to about 14 carbon atoms, about 6 to 16 carbon atoms, about 8 to 12 carbon atoms, or about 6 to about 10 carbon atoms. In one embodiment, the polymer comprises a repeating unit with the structure of Figure X, and the polymer breaks down over a period of months into salicylic acid as demonstrated in Figure 28. The polymer may be a polyazo. In one embodiment, the polymer comprises one or more monomer units of the chemical

formula (XI) $-A-R^1-N=N-R^1-(A-L)_n$ (XI), and/or the chemical frormula $-(A-R^1-N=N-R^1-(A-L)_n)_x$ (XII), wherein each R^1-N is a group that will provide a biologically active compound upon hydrolysis of the polymer; each A comprises anhydride, amide, thioamide, thioester, or ester; and L is a linking group; where n is 0 or 1 and x represents the number of repeating groups, e.g. x may be an integer from 2 to about 100, preferably from 2 to about 50, and more preferably, from 5 to 50). Suitable monomers are polymerized to provide the polyazo compounds. In one embodiment, the polyazo compound is a compound containing at least one free amine group to form the azo group and at least one free carboxylic acid group, alcohol group or amine group available for reactions which may self-polymerize or co-polymerize with carboxylic acid groups or bis(acyl) chlorides. In one embodiment, the polymer comprises an active agent incorporated in a poly(azo-anhydride). In one embodiment, the polymer comprises a polymeric drug delivery system for oral delivery of a drug comprising a poly(azo-anhydride) where the drug is 5-ASA or 4-ASA. The polymer may have two, three, or more different R groups that will each provide a different active agent upon hydrolysis of the polymer. Such polymers are particularly useful for the administration of a combination of two or more active agents to a host, such as an animal or plant. The polymer may be a homopolymer, or a co-polymer. The polymer of the invention typically have a glass transition temperature (Tg) about –10, -5, 0, 10, 30, 50 to about 60, 70, 80, 100, 130, 160, 200 C. One preferred group of polymers is that where the glass transition temperature Tg is in the vicinity of about 50 C. The polymer may comprise any number of agents, whether biologically, diagnostically, therapeutically active or inactive, or whether they have other activities that make them suitable for applications other than to microorganisms, plants, animas or humans. In fact any type of agent that may be polymerized or mixed, dispersed or otherwise incorporated into a polymeric formulation, and released from its large molecular weight structure is suitable for use in this application. Such agent(s) may be loaded in amounts of about 0, 5, 10, 15, 20 %w/w to about 25, 30, 35, 40, 45, 50 %w/w, although other amounts are also contemplated. In one preferred embodiment, the polymer comprises a non-steroidal anti-inflammatory agent (NSAID), such as, e.g., salicylic acid and/or diflunisal. Such polymers include for example, polymers comprising repeating units of Formula II, Formula III, Formula VII and/or Formula X. NSAIDs are thought to block the fever, swelling, redness and pain associated with inflammation. In one embodiment, the polymer is combined with one or more agents in any suitable manner, such as, e.g. by physically admixing, embedding, appending, or dispersing the active agent in the polymer matrix. The agent(s) may be added to the backbone, chemically linked in the backbone through a linker or spacer molecule, directly or indirectly chemically linked to a chemical group attached to the backbone of the polymer and/or electrostatically, or in any other manner attached to the polymer or the polymer backbone. In one embodiment, the active agents may be attached to repeating units of the polymers of the present invention by covalent bonds linked to an Ar ring or an R organic moiety, providing for sustained release of the agent, e.g. an active agent, or it may merely reside in the unoccupied spaces present in the polymer. In another embodiment, the active agent forms a salt with the polymer or the polymer backbone. In one embodiment, the agent is located in the unoccupied spaces of a polymer and is present as a homogeneous functional group or it may be incorporated into a salt, micelle, liposome, or heterogeneous aggregate. The polymer may comprise a polymer backbone that comprises one or more similar or different residues comprising an agent(s) that will be released either directly or indirectly, for instance by hydrolysis or enzymatic degradation of the polymer. In addition, the polymer may also comprise a second or additional agent that is physically admixed, embedded or dispersed in, or combined with the polymer as is known in the art. In one embodiment, the polymer comprises units of the chemical structure of Formula (III), where the agent comprises an NSAID, and also comprises an NSAID physically admixed, embedded or dispersed in the polymer matrix.

The polymers of the invention may be prepared by any suitable method known in the art. Examples are those described in International Patent Application WO 99/12990; U.S. Patent Applications No. 09/917,231; 09/917,194; 09/508,217; 09/422,294; 09/732,516; 60/220,707; 60/261,337; 60/058,328; and 60/220,998; and Conix, Macromol. Synth. 2: 95-99 (1966). The polymer may be formulated so that it will be released over an extended period of time when administered in accordance with the invention, e.g. over at least about 2, 5, 7, 10, 20, 40, 60, 80, 100, 120, 140, 160, 180 to about 200, 220, 240, 260, 280, 300, 320, 340, 360 days, and even over longer periods of time. For example, when applied for treatment of hard tissue the polymer may be formulated for release over a period of about 30 to about 90 days; for treatment of soft tissue about 1, 2, 5, 10 to about 12, 15, 20, 30 days, or over about 1 to 2 years. A polymer of this invention may have for example properties compatible with dosage of drug delivered, pharmacokinetics, rate of generation, elution or release, duration of release, elution or generation of the drug, agent solubility and binding characteristics to other agents and substances in the environment, another agent interaction, e.g. drug interaction. The polymer may have properties compatible with the physical, chemical, and/or biological requirements for matching the environment for which it is intended, e.g. coating with the surface and bulk of a medical or veterinary device, such as the coating's adherence to the surface of the implanted medical device during processing/coating as well as during implantation, coating stability on the device, coating reproducibility and reliability, non-planar coating ability, porous, and textured geometries, the void filling ability for providing agent reservoirs, and the ability of the coating to withstand mechanical e.g. tensile, compressive, torsional, and shear, and frictional forces generated during coating processing/application, implantation and subsequent use. One example is the behavior of a coating during subsequent tissue response of an implanted medical or veterinary device.

<u>Linking Group (L)</u>

The polymer of the invention may comprise a linking group(s) that may be present in the polymer backbone along with the agent(s) through bonds that release the agent(s) under certain environmental conditions. Examples of bonds are esters, thioesters, amides, thioamides, urethanes, carbamates, thiocarbamates, carbonates, thiocarbonates, and any others than fulfill the function. This includes combinations and mixtures thereof. The linking bonds may comprise other groups, and atoms, including P, C, O, S, halogens, metals, and other inorganic and organic atoms provided that they form labile bonds that may release under appropriate circumstances the agent(s) within the backbone, and the agent(s) mixed into the polymer. The linking group(s) may be selected as well to impart to the polymer desirable physical, chemical, and/or biological properties. Examples of these are adhesion to metallic, polymeric, ceramic or glassy surfaces on implantable medical and veterinary devices to allow formation of a coating that may withstand handling, implantation, and exposure to body tissues and/or fluids post-implantation; sufficient mechanical strength, flexibility, and ability to withstand without failure application of mechanical stress without failure; minimal stickiness on the surface of the resulting coating to minimize adhesion to vehicles used in the delivery or implantation of the medical or veterinary device in the body of a human or animal; and the ability to sterilize the coating and the associated medical or veterinary device by the application of gamma irradiation, electron beam (E beam), treatment with ethylene oxide, or other chemical or physical treatments providing sterilization. Suitable linking groups are widely known in the art, and need not be fully detailed here. Examples are described in U.S. Patent Nos. 6,613,807; 6,328,988; 6,365,146; 6,468,519; 6,486,214; 6,497,895; 6,602,915; 6,613,807; U.S. Published Patent Applns. 2002/0071822 A1; 2002/0106345 A1; 2003/0035787 A1; 2003/0059469 A1; 2003/0104614 A1; 2003/0170202 A1;

U.S.S.Ns. 09/508,217; 10/368,288; 10/622,072; 10/646,336; 10/647,701; and International Patent Applications WO 99/12990; WO 01/28492; WO 01/41753; WO 01/58502; WO 02/09767; WO 02/09768; WO 02/09769; WO 03/005959; WO 03/046034; WO 03/065928; and WO 03/072020. The nature of the linking group (L) in a polymer of the invention may be employed to provide the polymer of the invention with one or more desirable physical, chemical, and/or biological properties, such as mechanical and thermal properties; adhesiveness; wettability; hardness; drug generation, and release kinetics and solubility; and tissue compatibility and response for the selected therapeutic application. The linking group L is typically a divalent organic radical having a molecular weight (MW) about 25, 40 daltons to about 200, 400 daltons. The mechanical and degradative properties, e.g. hydrolytic properties, of the polymer of the invention may be controlled by incorporating and/or modifying a specific linking group (L) into the polymer backbone. The molecular weight and chemical composition of the linking group may affect the polymer's glass transition temperature (Tg), and accordingly, the mechanical properties of the therapeutic polymers and coatings of the therapeutic polymers at body temperatures. The higher the molecular weight, the greater the toughness of the material in terms of elasticity and tear strength. The linking group may be biologically inactive, or may itself possess biological or other activity, and may comprise other functional groups. Examples of functional groups that the linker may have are hydroxy, mercapto, amine, carboxylic acid, halogen, aliphatic and aromatic hydrocarbons with and without heteroatoms, and many others useful for modifying the properties of the polymer, e.g. for branching, cross linking, increasing hydrophillicity or hydrophobicity, solubility, degradation rate, hardness, flexibility, elasticity, ability to append another agent(s) to the polymer, or biodistribution of the polymer, among many others. In one embodiment, the linker may have two or more functional groups that, among others, may be hydroxy -OH, mercapto -SH or SR, amine –NH- or –NR-, carboxylic acid -COOH, and many others that form degradable bonds with the agent(s) to be polymerized, e.g. hydrolyzed, or cleaved by proteolytic, or other biological of biochemical processes when placed in contact with body tissues or fluids. L may be an amino acid, a peptide, a nucleic acid, a carbohydrate or polysaccharide, or any other type of chemical structure. L generally comprises a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having about 3, 6, 8, 10, 12, 14 to about 16, 18, 20, 22, 25 carbon atoms, and at times more carbon atoms, wherein one or more, e.g. 1, 2, 3, or 4, carbon atoms is optionally replaced by (-O-) or (-NR-). L may be a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 25 carbon atoms, wherein the chain is optionally substituted on carbon with one or more, e.g. 1, 2, 3, or 4, substituents comprising (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy, or other functional groups. In one preferred embodiment, L comprises a dicarboxylic acid hydrocarbon chain with about 3, 4, 6, 8, 10 to about 12, 14, 16, 18, 22, 24, 26 carbon atoms, preferably an even number of carbon atoms that may be the same or different. This linker may be used with any suitable active agent, such as, e.g., salicylic acid, diflunisal and/or a derivative thereof.

Active Agents

Any suitable agent may be employed in the polymers of the invention. In one embodiment, the active agents that may be incorporated into the polymers of the invention possess at least two functional groups that may each be incorporated into an ester, thioester, urethane, carbamate, carbonate or amide linkage of a polymer, such that, upon hydrolysis or enzymatic degradation of the polymer, the active agent is obtained. The functional groups may independently be a hydroxy group (-OH), a mercapto group (-SH), an amine group (-NHR), or a carboxylic acid (-COOH). These

functionalities form biodegradable bonds with the drug to be polymerized that are hydrolyzed, broken by proteolytic process, or broken by other biological of biochemical processes when placed in contact with body tissues or fluids. An active agent may also comprise other functional groups (including hydroxy groups, mercapto groups, amine groups, and carboxylic acids, as well as others) that may be used to modify the properties of the polymer (e.g. for branching, for cross linking, for appending other molecules (e.g. another active compound) to the polymer, for changing the solubility of the polymer, or for effecting the biodistribution of the polymer). One skilled in the art may readily select active agents that possess the necessary functional groups for incorporation into the polymers of the invention from these lists. The agent may comprise a biological, diagnostic, therapeutic, or other type of agent such as suitably functionalized analgesics, anesthetics, anti-acne agents, antibiotics, anti-cholinergics, anti-coagulants, anti-convulsants, anti-diabetic agents, anti-dyskinetics, antifibrotic agents, antifungal agents, anti-glaucoma agents, anti-infectives, anti-inflammatory compounds, antimicrobial compounds, anti-neoplastics, anti-Parkinson's agents, antiosteoporotics, antiseptics, antisporatics, antithrombotics, antiviral compounds, bacteriostatic compounds, bone resorption inhibitors, calcium regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, deodorants, disinfectants, dopamine receptor agonists, erectile dysfunction agents, fertility agents, gastrointestinal agents, gout agents, hormones, hypnotics, immunomodulators, immunosuppressives, keratolytics, migraine agents, motion sickness agents, muscle relaxants, nucleoside analogs, obesity agents, opthalmic agents, bone healing, osteoporosis agents, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sclerosing and anti-sclerosing agents, sedatives, skin and mucous membrane agents, smoking cessation agents, sympatholytics, ultraviolet screening agents, urinary tract agents, vaginal agents, contraceptives, hormones, sexual function aid agents, and vasodilators. See, Physicians' Desk Reference, 55 Ed., Medical Economics Company, Inc., Montvale, New Jersey, pages 201-202 (2001). Suitable active agents may be found, for example, in: Physician's Desk Reference, 55 ed., 2001, Medical Economics Company, Inc., Montvale, New Jersey; USPN Dictionary of USAN and International Drug Names, 2000, The United States Pharmacopeial Convention, Inc., Rockville, Maryland; and The Merck Index, 12 ed., 1996, Merck & Co., Inc., Whitehouse Station, New Jersey.

Examples of suitable agents are 2-p- sulfanilyanilinoethanol; 3-amino-4-hydroxybutyric acid; 4,4'-sulfinyldianiline; 4-sulfanilamidosalicylic acid; 6-azauridine; 6-diazo-5-oxo-L-norleucine; 6-mercaptopurine; aceclofenac; acediasulfone; acetosulfone; aclacinomycin(s); acriflavine; acyclovir; albuterol; alendronate; alminoprofen; amfenac; amicarbilide; amikacin; aminoquinuride; amiprilose; amoxicillin; amphotericin B; ampicillin; ancitabine; anthramycin; apalcillin; apicycline; apramycin; arbekacin; argatroban; arsphenamine; aspoxicillin; atorvastatin; azacitadine; azaserine; azidamfenicol; azithromycin; aztreonam; bacitracin; bambermycin(s); benazepril; bialamicol; biapenem; bleomycin(s); brodimoprim; bromfenac; bromosaligenin; bucillamine; budesonide; bumadizon; buprenorphine; butethamine; butirosin; butorphanol; candicidin(s); capecitabine; capreomycin; captopril; carbenicillin; carbomycin; carboplatin; carprofen; carubicin; carumonam; carzinophillin A; cefaclor; cefadroxil; cefamandole; cefatrizine; cefbuperazone; cefclidin; cefdinir; cefditoren; cefepime; cefetamet; cefixime; cefmenoxime; cefminox; cefodizime; cefonicid; cefoperazone; ceforanide; cefotaxime; cefotetan; cefotiam; cefozopran; cefpimizole; cefpiramide; cefpirome; cefprozil; cefroxadine; ceftazidime; cefteram; ceftibuten; ceftriaxone; cefuzonam; cephalexin; cephaloglycin; cephalosporin C; cephradine; chloramphenicol; chloroazodin; chloroazodin; chlorozotocin; chlorphenesin; chlortetracycline; chromomycin(s); cilastatin; ciprofloxacin; cladribine; clarithromycin; clinafloxacin; clindamycin; clomocycline; colistin; coumetarol; cyclacillin;

cyclosporin; cytarabine; dapsone; daunorubicin; demeclocycline; denopterin; dermostatin(s); diathymosulfone; dibekacin; diclofenac; dicoumarol; diflunisal; dihydrostreptomycin; dirithromycin; ditazol; docetaxel; dopamine; doxifluridine; doxorubicin; doxycycline; edatrexate; eflornithine; elliptinium; enalapril; enfenamic acid; enocitabine; enoxacin; enviomycin; epicillin; epirubicin; erythromycin; ethyl biscoumacetate; ethylidene; etodolac; etofenamate; etoposide; famotidine; fenalcomine; fendosal; fepradinol; filipin; flomoxef; floxuridine; fludarabine phosphate; flufenamic acid; fluvastatin; fortimicin(s); fungichromin; gemcitabine; gentamicin(s); gentisic acid; glucamethacin; glucosulfone; glycol salicylate; gramicidin S; gramicidin(s); grepafloxacin; guamecycline; gusperimus; hetacillin; hydroxytetracaine; idarubicin; iloprost; imipenem; indinavir; isepamicin; josamycin; kanamycin(s); lamifiban; lamivudine; leucomycin(s); leuprolide; lincomycin; lisinopril; lisinpril; lomefloxacin; lucensomycin; lymecycline; mannomustine; meclocycline; meclofenamic acid; mefenamic acid; melphalan; menogaril; mepartricin; meropenem; mesalamine; metformin; methacycline; methotrexate; methsalamine; metoprolol; micronomicin; midecamycin(s); minocycline; mitobronitol; mitolactol; mitomycin C; mitoxantrone; mopidamol; morphine; moxalactam; mupirocin; mycophenolic acid; nadifloxacin; naepaine; nalbuphine; natamycin; neomycin; netilmicin; niflumic acid; nizatidine; nogalamycin; norfloxacin; nystatin; oleandomycin; oligomycin(s); olivomycin(s); olsalazine; orthocaine; oxaceprol; oxymorphone; oxytetracycline; paclitaxel; panipenem; paromomycin; pazufloxacin; penicillin N; pentostatin; peplomycin; perimycin A; phenamidine; pipacycline; pipemidic acid; pirarubicin; piridocaine; piritrexim; plicamycin; podophyllinic acid 2-ethylhydrazine; polymyxin; pravastatin; prednimustine; primycin; procarbazine; procodazole; p-sulfanilylbenzylamine; pteropterin; puromycin; quinacillin; quinapril; ranimustine; ranitidine; ribostamycin; rifamide; rifampin; rifamycin SV; rifapentine; rifaximin; ristocetin; ritipenem; rokitamycin; rolitetracycline; romurtide; rosaramycin; roxithromycin; S-adenosylmethionine; salazosulfadimidine; salicyl alcohol; salicylic acid; salmeterol; salsalate; sancycline; sirolimus (rapamycin); sisomicin; solasulfone; sparfloxacin; spectinomycin; spiramycin; streptomycin; streptonigrin; streptozocin; succisulfone; sulfachrysoidine; sulfaloxic acid; sulfamidochrysoidine; sulfanilic acid; sulfasalazine; sulfoxone; tacrolimus; taprostene; teicoplanin; temafloxacin; temocillin; teniposide; tetracycline; tetroxoprim; thiamiprine; thiamphenicol; thiazolsulfone; thioguanine; thiostrepton; ticarcillin; tigemonam; tioclomarol; tirofiban; tobramycin; tolfenamic acid; Tomudex7 (N - [[5 -[[(1, 4-Dihydro-2-methyl-4-oxo-6- quinazolinyl) methyl] methylamino] -2-thienyl] carbonyl] -L-glutamic acid), topotecan; tosufloxacin; trimethoprim; trimetrexate; trospectomycin; trovafloxacin; tuberactinomycin; tubercidin; ubenimex; vancomycin; vinblastine; vincristine; vindesine; vinorelbine; xinafoate; zidovudine; zorubicin; and any enantiomers, derivatives, bases, salts or mixtures thereof.

In one embodiment, the active agent comprises a non-steroidal anti-inflammatory drug (NSAID) such as those described in U.S.S.N. 09/732,516, filed 07 December 2000; 3-amino-4-hydroxybutyric acid, aceclofenac, alminoprofen, amfenac, bromfenac, bromosaligenin, bumadizon, carprofen, diclofenac, diflunisal, ditazol, enfenamic acid, etodolac, etofenamate, fendosal, fepradinol, flufenamic acid, gentisic acid, glucamethacin, glycol salicylate, meclofenamic acid, mefenamic acid, mesalamine, niflumic acid, olsalazine, oxaceprol, S-adenosylmethionine, salicylic acid, salsalate, sulfasalazine, tolfenamic acid and the like. In one embodiment, the active agent is an anti-bacterial, for example, 2-p- sulfanilyanilinoethanol, 4,4'-sulfinyldianiline, 4-sulfanilamidosalicylic acid, acediasulfone, acetosulfone, amikacin, amoxicillin, amphotericin B, ampicillin, apalcillin, apicycline, apramycin, arbekacin, aspoxicillin, azidamfenicol, azithromycin, aztreonam, bacitracin, bambermycin(s), biapenem, brodimoprim, butirosin, capreomycin, carbenicillin, carbomycin, carumonam, cefadroxil, cefamandole, cefatrizine, cefbuperazone, cefclidin, cefdinir, cefditoren,

cefepime, cefetamet, cefixime, cefmenoxime, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefotiam, cefozopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, ceftazidime, cefteram, ceftibuten, ceftriaxone, cefuzonam, cephalexin, cephaloglycin, cephalosporin C, cephradine, chloramphenicol, chlortetracycline, ciprofloxacin, clarithromycin, clinafloxacin, clindamycin, clomocycline, colistin, cyclacillin, dapsone, demeclocycline, diathymosulfone, dibekacin, dihydrostreptomycin, dirithromycin, doxycycline, enoxacin, enviomycin, epicillin, erythromycin, flomoxef, fortimicin(s), gentamicin(s), glucosulfone solasulfone , gramicidin S, gramicidin(s), grepafloxacin, guamecycline, hetacillin, imipenem, isepamicin, josamycin, kanamycin(s), leucomycin(s), lincomycin, lomefloxacin, lucensomycin, lymecycline, meclocycline, meropenem, methacycline, micronomicin, midecamycin(s), minocycline, moxalactam, mupirocin, nadifloxacin, natamycin, neomycin, netilmicin, norfloxacin, oleandomycin, oxytetracycline, p- sulfanilylbenzylamine, panipenem, paromomycin, pazufloxacin, penicillin N, pipacycline, pipemidic acid, polymyxin, primycin, quinacillin, ribostamycin, rifamide, rifampin, rifamycin SV, rifapentine, rifaximin, ristocetin, ritipenem, rokitamycin, rolitetracycline, rosaramycin, roxithromycin, salazosulfadimidine, sancycline, sisomicin, sparfloxacin, spectinomycin, spiramycin, streptomycin, succisulfone, sulfachrysoidine, sulfaloxic acid, sulfamidochrysoidine, sulfanilic acid, sulfoxone, teicoplanin, temafloxacin, temocillin, tetracycline, tetroxoprim, thiamphenicol, thiazolsulfone, thiostrepton, ticarcillin, tigemonam, tobramycin, tosufloxacin, trimethoprim, trospectomycin, trovafloxacin, tuberactinomycin, vancomycin and the like.

In still another embodiment, the active agent comprises an anti-fungal agent such as amphotericin B, azaserine, candicidin(s), chlorphenesin, dermostatin(s), filipin, fungichromin, lucensomycin, mepartricin, natamycin, nystatin, oligomycin(s), perimycin A, tubercidin, and the like. In another embodiment the active agent comprises an anti-cancer, e.g., carcinomas, sarcomas, leukemias and cancers derived from cells of the nervous system), including anti-neoplastic, for example, 6-azauridine, 6-diazo-5-oxo-L-norleucine, 6-mercaptopurine, aclacinomycin(s), ancitabine, anthramycin, azacitadine, azaserine, bleomycin(s), capecitabine, carubicin, carzinophillin A, chlorozotocin, chromomycin(s), cladribine, cytarabine, daunorubicin, denopterin, docetaxel, doxifluridine, doxorubicin, edatrexate, eflornithine, elliptinium, enocitabine, epirubicin, etoposide, floxuridine, fludarabine, gemcitabine, idarubicin, mannomustine, melphalan, menogaril, methotrexate, mitobronitol, mitolactol, mitomycin C, mitoxantrone, mopidamol, mycophenolic acid, nogalamycin, olivomycin(s), paclitaxel, pentostatin, peplomycin, pirarubicin, piritrexim, plicamycin, podophyllinic acid 2- ethylhydrazine, prednimustine, procarbazine, pteropterin, puromycin, ranimustine, streptonigrin, streptozocin, teniposide, thiamiprine, thioguanine, Tomudex□ (N-[[5- [[(1,4-Dihydro-2-methyl-4-oxo-6-quinazolinyl)methyl]methylamino]-2- thienyl]carbonyl]-L-glutamic acid), toptecan, trimetrexate, tubercidin, ubenimex, vinblastine, vindesine, vinorelbine, zorubicin and the like. In yet another embodiment, the active agent comprises an anti-thrombotic, for example, argatroban, coumetarol, dicoumarol, ethyl biscoumacetate, ethylidene dicoumarol, iloprost, lamifiban, taprostene, tioclomarol, tirofiban and the like. The agent may also comprise an immunosuppressive, for example, 6- mercaptopurine, amiprilose, bucillamine, gusperimus, mycophenolic acid, procodazole, romurtide, sirolimus (rapamycin), tacrolimus, ubenimex and the like; a general or local anesthetic such as butethamine, fenalcomine, hydroxytetracaine, naepaine, orthocaine, piridocaine, salicyl alcohol and the like, and many others whose list is too extensive to incorporate into the text of this patent.

In one embodiment, the active agent is a low molecular weight drug suitable for linkage into degradable copolymers via a polyanhydride. Such low molecular weight drugs typically have a relatively low molecular weights of approximately 1,000 daltons or less, and may comprise one or more of a carboxylic acid (-COOH), amine (-NH-, -NR-), thiol (-SH, -SR-), alcohol (-OH), phenol (-Ph-OH), ester (-COO-), carbonate (OCOO-), or others that are suitable as well. Suitable examples of low molecular weight drugs with the required functional groups within their structure may be found in almost all classes of drugs including, but not limited to, analgesics, anesthetics, antiacne agents, antibiotics, synthetic antibacterial agents, anticholinergics, anticoagulants, antidyskinetics, antifibrotics, antifungal agents, antiglaucoma agents, anti- inflammatory agents, antineoplastics, antiosteoporotics, antipagetics, anti-Parkinson's agents, antisporatics, antipyretics, antiseptics/disinfectants, antithrombotics, bone resorption inhibitors, calcium regulators, keratolytics, sclerosing agents and ultraviolet screening agents. Particularly important classes of agents are analgesics, anesthetics, antiacne agents, antibiotics, anticancer agents, anticholinergics, anticoagulants, anticonvulsants, antidiabetic agents, antidyskinetics, antifibrotic agents, antifungal agents, antiglaucoma agents, anti-infectives, anti-inflammatory compounds, antimicrobial compounds, antineoplastics, anti-Parkinson's agents, antiosteoporotics, antiseptics, antisporatics, antithrombotics, antiviral compounds, bacteriostatic compounds, bone resorption inhibitors, calcium regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, deodorants, disinfectants, dopamine receptor agonists, agents for the treatment of erectile dysfunction, fertility agents, agents for the treatment of gastrointestinal ailments, agents for the treatment of gout, hormones, hypnotics, immunomodulators, immunosuppressives, keratolytics, agents for the treatment of migraine, agents for the treatment of motion sickness, muscle relaxants, nucleoside analogs, agents for the treatment of obesity, opthalmic agents, osteoporosis agents, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, agents for the treatment of respiratory ailments, agents for the treatment of sclerosis, sedatives, agents for the treatment of skin and muscous membrane ailments, smoking cessation agents, sympatholytics, ultraviolet screening agents, agents for the treatment of urinary ailments, agents for the treatment of vaginal ailments, and vasodilators.

Medical Devices, Compositions and Therapeutic Methods

The polymers of the invention are generally bioerodable, and biocompatible, and are useful in a variety of applications where delivery of an active agent or agents is desired. In one embodiment, the polymers described herein may be used to form, coat or otherwise treat medical devices. The medical device of the invention may be any suitable medical device, such as an implantable device. The polymers of the invention may be employed for forming or coating shaped articles such as stents and grafts, e.g. vascular grafts and stents, plates e.g. bone, dental, and orthodontic plates, sutures, wound closing staples, stitches, surgical meshes, dental and bone implants, implantable sensors, cuffs, pins, sutures, implantable drug delivery and sensory or diagnostic devices, stents for tissue regeneration, and other articles suitable for implantation into a patient. Suitable medical devices include, for example, stents, e.g., coronary vascular stents, peripheral vascular stents, free standing films of 0.1mm to about 1-2 mm suitable for surgical coverings, solutions, suspensions, emultions, sprays, creams, gels, in situ solidifying formulations, and semi-liquid and liquid formulations for "painting surgically treated areas, urethral stents, biliary stents, stents used for supporting the lumen of other anatomical tubes, and stents used for other medical treatments; catheters, e.g., surgical catheters and urinary catheters; grafts; and orthopedic implants including, e.g., hip, knee and shoulder implants, internal and external fixation devices and spinal cages, dental tooth implants, dry sockets, biosensor

implants e.g. for preventing fibrosis, ophthalmic implants and replacements, prolene mesh or thread, eye drops e.g. non crystalline formulation, marine coatings, cervical rings e.g. for contraception or sexual enhancement, other women's health applications, anti-infective coating on health aids such as bandages of the sort shown in US patent 5,814,031, dental applications e.g. fibrous and coated floss, cosmetic surgery fillers, e.g. botox, collagen, hyaluronic acid, etc., fiber, strand form for sutures, dermabrasion treatments, wrinkle reduction, acne e.g. with retinoic acid, breast implants, adhesions, capsular contracture, employing products such as pivucane (APP Pharma), injectable formulations e.g. Injectile Technologies, all of the relevant information relating to these products from publically available sources being incorporated herein by reference.

Medical devices useful with coverings of the present invention include, but are not limited to, a fixation device, catheters, drain tubes, intravenous tubes, tampon applicators, ventilator tubes, endoscopes, arthroscopes, IUDs and other drug-based contraceptive implants and patches of all sorts for drug delivery, e.g. hormones, nicotine, and other patches, needles, condoms, barrier devices, diagnostic devices such as a speculum, dental appliances, and surgical appliances. The polymers, compounds and/or compositions of the invention may be formed into a medical implant such as a medical, dental, orthopedic and surgical implant, or applied or coated onto such implant. In addition to the implants described above, other examples are implants for vascular, cardiovascular, coronary, peripheral vascular, orthopedic, dental, oro-maxillary, gastrointestinal, urogenital, ophthalmic, gynecological, pulmonary, surgical, physiological, metabolic, neurological, diagnostic and therapeutic uses, may be formed from or applied or coated with the above identified polymers, compounds and/or compositions. Such implants include, but are not limited to, stents, catheters, balloons, guidewires, grafts, sutures, meshes, joint prostheses, breast prostheses, fracture management devices, drug dosing devices, pacemakers, mechanical pumps, dental implants (e.g., dental, oro-maxillary, and alveolar), defibrillators, and filters.

Suitable medical implants also include, but are not limited to the ones described here. 1) Boston Scientific (Boston Scientific Corporation, Natick, MA) products Polaris™, NIR® Elite OTW Stent System, NIR® Elite Monorail(™) Stent System, Magic WALLSTENT® Stent System, Radius® Self Expanding Stent, NIR® Biliary Stent System, NIROYAL(™) Biliary Stent System, WALLGRAFT® Endoprosthesis, WALLSTENT® Endoprosthesis, RX Plastic Biliary Stents, UroMax Ultra (™) High Pressure Balloon Catheter, Passport (™) Balloon on a Wire Catheter, Excelsior(™) 1018(™) Microcatheter, Spinnaker® Elite(™) Flow-Directed Microcatheter, Guider Softip(™) XF Guide Catheters, Sentry(™) Balloon Catheters, Flexima(™) APD(™) Drainage Catheters with Twist Loc(™) Hub, Vaxcel(™) Chronic Dialysis Catheter, PASV® PICC Peripherally Inserted Central Catheters, Chilli® Cooled Ablation Catheters, and Constellation® Catheters. 2) Cordis (Cordis, a Johnson & Johnson Company, Piscataway NJ) products: BX Velocity(™) Coronary Stents, Ninja FX(™) Balloon Catheters, Raptor (™) Balloon Catheters, NC Raptor(™) Balloon Catheters, Predator(™) Balloon Catheters, Titan Mega(™) Balloon Catheters, Checkmate(™) Brachytherapy Catheters, Infiniti(™) Diagnostic Catheters, Cinemayre(™) Diagnostic Catheters, SuperTorque Plus(™) Diagnostic Catheters, and High Flow(™) Diagnostic Catheters. 3) Medtronics (Medtronics, Inc., Minneapolis, MN) products: Aneurx Stentgraft, S7 Coronary Stents, S670 Coronary Stents, S660 Coronary Stents, BeStent 2 Coronary Stents, D1 Balloon Catheters, and D2 Balloon Catheters. 4) Avantec Vascular (Avantec Vascular, San Jose, CA) products: Duraflex(™) Coronary Stent System, and Apollo (™) Coronary Dilatation Catheter. 4) B. Braun (B.Braun Medical Ltd., Sheffield, England) products: Coroflex(™) Coronary Stent, Cystofix(™) Urogenital Catheters, and Urecath(™) Urogenital Catheters. 5) Cook (Cook Group Inc.,

Bloomington, IN.) products: V-Flex Plus(™) Coronary Stent, and CR II® Coronary Stent. 6) Guidant (Guidant Corporation, Indianapolis, IN) products: Multilink Penta(™) Coronary Stents, Multilink Pixel(™) Coronary Stents, Multilink Ultra(™) Coronary Stents, Multilink Tetra(™) Coronary Stents, Multilink Tristar (™) Coronary Stents, Ancure (™) Stentgraft, Dynalink (™) Biliary Stents, Rx Herculink(™) Biliary Stents, Omnilink(™) Biliary Stents, Megalink(™) Biliary Stents, Rx Crosssail(™) Balloon Dilatation Catheters, Rx Pauersail(™) Balloon Dilatation Catheters, OTW Opensail(™) Balloon Dilatation Catheters, OTW Highsail(™) Balloon Dilatation Catheters, Rx Esprit (™) Balloon Dilatation Catheters, Rx Viatrac(™) Peripheral Catheters, and OTW Viatrac(™) Peripheral Catheters. 7) Ethicon (Ethicon, a Johnson & Johnson Company, Piscataway, N.J.) products: Vicryl™ (resorbable braided coated), Pronova™, and Panacryl™. 8) USS/DG Sutures (U.S. Surgical, a division of Tyco Healthcare Group LP, Norwalk, CT) products: Decon II™ (coated, braided synthetic, absorbable), PolySorb™ (coated, braided synthetic, absorbable), Dexon S™ (Uncoated, braided synthetic, absorbable), Gut sutures (absorbable), Biosyn™ (synthetic monofilament, absorbable), Maxon™ (synthetic monofilament, absorbable), Surgilon™ (braided nylon, non-absorbable), Ti-Cron™ (coated, braided polyester, non-absorbable), Surgidac™ (coated, braided polyester, non-absorbable), SofSilk™ (coated, braided silk, non-absorbable), Dermalon™(nylon monofilament, non-absorbable), Monosof™ (nylon monofilament, non-absorbable), Novafil™ (polybutester monofilament, non-absorbable), Vascufil™ (coated polybutester monofilament, non-absorbable), Surgilene™ (polypropylene monofilament, non-absorbable), Surgipro™ (polypropylene monofilament, non-absorbable), Flexon™ (stainless steel monofilament, non-absorbable), SURGALLOY™ needle, and SURGALLOY™ OptiVis™ needle. 9) Surgical Dynamics (Surgical Dynamics, Inc., North Haven, Connecticut,) products: S*D*Sorb™ (suture anchor, AnchorSew™ (suture anchor), S*D*Sorb E-Z Tac™ (bio-resorbable implant w/o sutures), S*D*Sorb Meniscal Stapler™ (delivers bio-absorbable repair implant), Ray Threaded Fusion Cage™ (spine), Aline™ (cervical plating system), SecureStrand™ (spinal reconstruction cable), and Spiral Radius 90D™ (spinal rod system). 10) Zimmer (Zimmer, Warsaw, Indiana) products: VerSys™ cemented stem hip system, VerSys Heritage™ Hip cemented stem hip system, VerSys™ LD/Fx cemented stem hip system, CPT™ Hip cemented stem hip system, VerSys™ Cemented Revision/Calcar cemented stem hip system, Mayo™ Hip porous stem hip system, VerSys™ Beaded MidCoat porous stem hip system, VerSys™ Beaded FullCoat Plus porous stem hip system, VerSys™ Fiber Metal MidCoat porous stem hip system, and VerSys™ Fiber Metal Taper porous stem hip system, VerSys™ LD/Fx press-fit hip system, VerSys™ Cemented Revision/Calcar revision stem hip system, ZMR™ hip revision stem hip system, Trilogy™ Cup acetabular cup hip system, ZCA™ cup acetabular cup hip system, Longevity™ polyethylene hip system, Calcicoat™ coating hip system, NexGen™ Implant knee system, NexGen™ Instruments knee system, NexGen™ Revision Instruments knee system, IM™ Instruments knee system, MICRO-MILL™ 5-in-1 Instruments knee system, Multi-Reference™ 4-in-1 knee system, V-STAT™ Instruments knee system, Coonrad/Morrey™ elbow, Bigliani/Flatow™ shoulder, Cable Ready™ Cable Grip System, Collagraft™ Bone Graft Matrix, Herbert™ Bone Screw, M/DN™ Intramedullary Fixation, Mini Magna-Fx™ Screw Fixation, Magna-Fx™ Screw Fixation, Periarticular™ Plating System, Versa-Fx ™Femoral Fixation system, Versa-Fix II™ Femoral Fixation System, and Trabecular™ Metal. 11) Alza technologies (ALZA Corporation, Mountain View, CA) products: DUROS® Implant, OROS™ osmotic, D-TRANS™ transdermal, STEALTH™ liposomal, E-TRANS™ electrotransport, Macroflux™, and ALZAMER depot. 12) described in Stuart, M., "Technology Strategies, Stent and Deliver," Start-Up, Windhover's Review of Emerging Medical Ventures, pp. 34-38, June 2000); van der Giessen, Willem J., et al. "Marked Inflammatory Sequelae to Implantation of Biodegradable

and Nonbiodegradable Polymers in Porcine Coronary Arteries," Circulation, Vol. 94, No. 7, pp. 1690-1697 (October 1, 1996); Gunn, J. et al., "Stent coatings and local drug delivery," European Heart Journal, 20, pp. 1693-1700 (1999); European Patent Applications: 01301671, 00127666, 99302918, 95308988, 95306529, 95302858, 94115691, 99933575, 94922724, 97933150, 95308988, 91309923, 91906591, and 112119841; PCT Publications: WO 00/187372, WO 00/170295, WO 00/145862, WO 00/143743, WO 00/044357, WO 00/009672, WO 99/03517, WO 99/00071, WO 98/58680, WO 98/34669, WO 98/23244, and WO 97/49434; U.S. Application Nos. 061568, 346263, 346975, 325198, 797743, 815104, 538301, 430028, 306785, and 429459; and U.S. Pat. Nos. 6,325,825, 6,325,790, 6,322,534, 6,315,708, 6,293,959, 6,289,568, 6,273,913, 6,270,525, 6,270,521, 6,267,783, 6,267,777, 6,264,687, 6,258,116, 6,254,612, 6,245,100, 6,241,746, 6,238,409, 6,214,036, 6,210,407, 6,210,406, 6,210,362, 6,203,507, 6,198,974, 6,190,403, 6,190,393, 6,171,277, 6,171,275, 6,165,164, 6,162,243, 6,140,127, 6,134,463, 6,126,650, 6,123,699, 6,120,476, 6,120,457, 6,102,891, 6,096,012, 6,090,104, 6,068,644, 6,066,125, 6,064,905, 6,063,111, 6,063,080, 6,039,721, 6,039,699, 6,036,670, 6,033,393, 6,033,380, 6,027,473, 6,019,778, 6,017,363, 6,001,078, 5,997,570, 5,980,553, 5,971,955, 5,968,070, 5,964,757, 5,948,489, 5,948,191, 5,944,735, 5,944,691, 5,938,682, 5,938,603, 5,928,186, 5,925,301, 5,916,158, 5,911,732, 5,908,403, 5,902,282, 5,897,536, 5,897,529, 5,897,497, 5,895,406, 5,893,885, 5,891,108, 5,891,082, 5,882,347, 5,882,335, 5,879,282, RE36,104, 5,863,285, 5,853,393, 5,853,389, 5,851,464, 5,846,246, 5,846,199, 5,843,356, 5,843,076, 5,836,952, 5,836,875, 5,833,659, 5,830,189, 5,827,278, 5,824,173, 5,823,996, 5,820,613, 5,820,594, 5,811,814, 5,810,874, 5,810,785, 5,807,391, 5,807,350, 5,807,331, 5,803,083, 5,800,399, 5,797,948, 5,797,868, 5,795,322, 5,792,415, 5,792,300, 5,785,678, 5,783,227, 5,782,817, 5,782,239, 5,779,731, 5,779,730, 5,776,140, 5,772,590, 5,769,829, 5,759,179, 5,759,172, 5,746,764, 5,741,326, 5,741,324, 5,738,667, 5,736,094, 5,736,085, 5,735,831, 5,733,400, 5,733,299, 5,728,104, 5,728,079, 5,728,068, 5,720,775, 5,716,572, 5,713,876, 5,713,851, 5,713,849, 5,711,909, 5,709,653, 5,702,410, 5,700,242, 5,693,021, 5,690,645, 5,688,249, 5,683,368, 5,681,343, 5,674,198, 5,674,197, 5,669,880, 5,662,622, 5,658,263, 5,658,262, 5,653,736, 5,645,562, 5,643,279, 5,634,902, 5,632,763, 5,632,760, 5,628,313, 5,626,604, 5,626,136, 5,624,450, 5,620,649, 5,613,979, 5,613,948, 5,611,812, 5,607,422, 5,607,406, 5,601,539, 5,599,319, 5,599,310, 5,598,844, 5,593,412, 5,591,142, 5,588,961, 5,571,073, 5,569,220, 5,569,202, 5,569,199, 5,562,632, 5,562,631, 5,549,580, 5,549,119, 5,542,938, 5,538,510, 5,538,505, 5,533,969, 5,531,690, 5,520,655, 5,514,236, 5,514,108, 5,507,731, 5,507,726, 5,505,700, 5,501,341, 5,497,785, 5,497,601, 5,490,838, 5,489,270, 5,487,729, 5,480,392, 6,325,800, 6,312,404, 6,264,624, 6,238,402, 6,174,328, 6,165,127, 6,152,910, 6,146,389, 6,136,006, 6,120,454, 6,110,192, 6,096,009, 6,083,222, 6,071,308, 6,048,356, 6,042,577, 6,033,381, 6,032,061, 6,013,055, 6,010,480, 6,007,522, 5,968,092, 5,967,984, 5,957,941, 5,957,863, 5,954,740, 5,954,693, 5,938,645, 5,931,812, 5,928,247, 5,928,208, 5,921,971, 5,921,952, 5,919,164, 5,919,145, 5,868,719, 5,865,800, 5,860,974, 5,857,998, 5,843,089, 5,842,994, 5,836,951, 5,833,688, 5,827,313, 5,827,229, 5,800,391, 5,792,105, 5,766,237, 5,766,201, 5,759,175, 5,755,722, 5,755,685, 5,746,745, 5,715,832, 5,715,825, 5,704,913, 5,702,418, 5,697,906, 5,693,086, 5,693,014, 5,685,847, 5,683,448, 5,681,274, 5,665,115, 5,656,030, 5,637,086, 5,607,394, 5,599,324, 5,599,298, 5,597,377, 5,578,018, 5,562,619, 5,545,135, 5,544,660, 5,514,112, 5,512,051, 5,501,668, 5,489,271, 6,319,287, 6,287,278, 6,221,064, 6,113,613, 5,984,903, 5,910,132, 5,800,515, 5,797,878, 5,769,786, 5,630,802, 5,492,532, 5,322,518, 5,279,563, 5,213,115, 5,156,597, 5,135,525, 5,007,902, 4,994,036, 4,981,475, 4,951,686, 4,929,243, 4,917,668, 4,871,356, 6,322,582, 6,319,445, 6,309,202, 6,293,961, 6,254,616, 6,206,677, 6,205,748, 6,178,622, 6,156,056, 6,128,816, 6,120,527, 6,105,339, 6,081,981, 6,076,659, 6,058,821, 6,045,573, 6,035,916, 6,035,751, 6,029,805, 6,024,757, 6,022,360, 6,019,768, 6,015,042, 6,001,121, 5,987,855, 5,975,876, 5,970,686, 5,956,927, 5,951,587, RE36,289, 5,924,561, 5,906,273, 5,894,921, 5,891,166, 5,887,706, 5,871,502, 5,871,490, 5,855,156, 5,853,423,

5,843,574, 5,843,087, 5,833,055, 5,814,069, 5,813,303, 5,792,181, 5,788,063, 5,788,062, 5,776,150, 5,749,898, 5,732,816, 5,728,135, 5,709,067, 5,704,469, 5,695,138, 5,692,602, 5,683,416, 5,681,351, 5,675,961, 5,669,935, 5,667,155, 5,655,652, 5,628,395, 5,623,810, 5,601,185, 5,571,469, 5,555,976, 5,545,180, 5,529,175, 5,500,991, 5,495,420, 5,491,955, 5,491,954, 5,487,216, 5,487,212, 5,486,197, 5,485,668, 5,477,609, 5,473,810, 5,409,499, 5,364,410, 5,358,624, 5,344,005, 5,341,922, 5,306,280, 5,284,240, 5,271,495, 5,254,126, 5,242,458, 5,236,083, 5,234,449, 5,230,424, 5,226,535, 5,224,948, 5,213,210, 5,199,561, 5,188,636, 5,179,818, 5,178,629, 5,171,251, 5,165,217, 5,160,339, 5,147,383, 5,102,420, 5,100,433, 5,099,994, 5,089,013, 5,089,012, 5,080,667, 5,056,658, 5,052,551, 5,007,922, 4,994,074, 4,967,902, 4,961,498, 4,896,767, 4,572,363, 4,555,016, 4,549,649, 4,533,041, 4,491,218, 4,483,437, 4,424,898, 4,412,614, D260,955, 4,253,563, 4,249,656, 4,127,133, D245,069, 3,972,418, 3,963,031, 3,951,261, 3,949,756, 3,943,933, 3,942,532, 3,939,969, 6,270,518, 6,213,940, 6,203,564, 6,191,236, 6,138,440, 6,135,385, 6,074,409, 6,053,086, 6,016,905, 6,015,427, 6,011,121, 5,988,367, 5,961,538, 5,954,748, 5,948,001, 5,948,000, 5,944,739, 5,944,724, 5,939,191, 5,925,065, 5,910,148, 5,906,624, 5,904,704, 5,904,692, 5,903,966, 5,891,247, 5,891,167, 5,889,075, 5,865,836, 5,860,517, 5,851,219, 5,814,051, 5,810,852, 5,800,447, 5,782,864, 5,755,729, 5,746,311, 5,741,278, 5,725,557, 5,722,991, 5,709,694, 5,709,692, 5,707,391, 5,701,664, 5,695,879, 5,683,418, 5,669,490, 5,667,528, 5,662,682, 5,662,663, 5,649,962, 5,645,553, 5,643,628, 5,639,506, 5,615,766, 5,608,962, 5,584,860, 5,584,857, 5,573,542, 5,569,302, 5,568,746, 5,566,822, 5,566,821, 5,562,685, 5,560,477, 5,554,171, 5,549,907, 5,540,717, 5,531,763, 5,527,323, 5,520,702, 5,520,084, 5,514,159, 5,507,798, 5,507,777, 5,503,266, 5,494,620, 5,480,411, 5,480,403, 5,462,558, 5,462,543, 5,460,263, 5,456,697, 5,456,696, 5,442,896, 5,435,438, 5,425,746, 5,425,445, 5,423,859, 5,417,036, 5,411,523, 5,405,358, 5,403,345, 5,403,331, 5,394,971, 5,391,176, 5,386,908, 5,383,905, 5,383,902, 5,383,387, 5,376,101, D353,672, 5,368,599, D353,002, 5,359,831, 5,358,511, 5,354,298, 5,353,922, 5,350,373, 5,349,044, 5,335,783, 5,335,775, 5,330,442, 5,325,975, 5,318,577, 5,318,575, 5,314,433, 5,312,437, 5,310,348, 5,306,290, 5,306,289, 5,306,288, 5,294,389, 5,282,832, 5,282,533, 5,280,674, 5,279,783, 5,275,618, 5,269,807, 5,261,886, 5,261,210, 5,259,846, 5,259,845, 5,249,672, 5,246,104, 5,226,912, 5,225,485, 5,217,772, 5,217,486, 5,217,485, 5,207,679, D334,860, 5,197,597, 5,192,303, D333,401, D333,400, 5,181,923, 5,178,277, 5,174,087, 5,168,619, 5,163,946, 5,156,615, 5,154,283, 5,139,514, 5,133,738, 5,133,723, 5,131,534, 5,131,131, 5,129,511, 5,123,911, 5,121,836, 5,116,358, 5,102,418, 5,099,676, 5,092,455, 5,089,011, 5,089,010, 5,087,263, 5,084,063, 5,084,058, 5,078,730, 5,067,959, 5,059,213, 5,059,212, 5,051,107, 5,046,513, 5,046,350, 5,037,429, 5,024,322, 5,019,093, 5,002,550, 4,984,941, 4,968,315, 4,946,468, 4,932,963, 4,899,743, and 4,898,156; the relevant portions of all of which are hereby incorporated by reference in their entireties.

Polymeric drug delivery systems comprising the polymers of the invention may be readily processed into pastes or solvent cast to yield films, coatings, nanoparticles e.g. nanospheres, microparticles e.g. microspheres and fibers with different geometric shapes for design of various medical devices, and may also be processed by compression molding and extrusion. In one embodiment, a polymer or polymers may be coated onto or applied onto a medical device, such as, e.g., by forming the polymer or polymers into a covering. In another embodiment, the polymer or polymers may be formed into a medical device, such as, e.g., an implant. In one embodiment of the present invention, a polymer comprising a functional group or active agent may used to form a covering, such as, e.g., a coating or a sheath, that partially or completely covers and/or surrounds a medical device. Such a covering may cover a portion of the medical device or it may completely cover a medical device. The covering may be divided into separate portions or several smaller coverings may be present on the medical device. In another embodiment of the invention, a polymer may surround the medical device, or a portion thereof, and may have the form of a coating, a layer, a

film, and combinations thereof. The polymer may be in the form of a solid or a semi-solid, such as a gel, sheath, a wrap, a tube or a cuff covering all or a portion of the medical device. The polymer may be rigid, semi-rigid, or non-rigid. The coating of polymer may comprise about 100 nm, 1 μm to about 1mm, 1 cm thick, although some porous implants may benefit from longer lasting effects enabled by a coating that completely fills the interstices of the device with, in some cases, a thin coating on those surfaces proximal to bone or other tissue upon placement in the body. In one embodiment, the polymer coating is comprised of microparticles, such as microspheres that may typically but not necessarily be less than 10 micron in diameter. These microparticles may be applied to the surface of a medical device before placement in the body. A sterile liquid may be used to coat the device to adhere such microspheres for minutes to weeks to enable uncoated medical devices to benefit from the same or similar therapeutic benefits as coated devices.

A polymer, compound and/or composition of the invention may be applied or coated onto a medical implant by any means known in the art including, but not limited to, solvent methods such as, for example, dipping and spray-drying, and non-solvent methods such as chemical vapor deposition, extrusion coating, covalently grafting or dipping in molten polymer, compound and/or composition of the invention. The method of preparation may vary depending on the polymer, compound and composition and/or the medical implant. The medical implant may be formed from or coated with one or more layers of the same or different polymer, compound and/or composition of the invention. In another example, a polymer, compound and/or composition of the invention may be coated onto a medical implant in the shape of a membrane or tube for use in the treatment of injury or damage to the peripheral nervous system or a block of solid or foamed composition containing pathways drilled or otherwise formed to encouraged nerve growth or bone growth. In the above instances, bioerosion of the disc, membrane, tube or block would yield or generate an active agent included within the polymer or composition. The polymer may be formed into a device by any means known in the art including, but not limited to, molding e.g. compression or blow molding, and extrusion. The medical device may be formed from one or more of the same or different polymer, compound and/or composition of the invention. A polymer, compound and/or composition of the invention may be formed, that is, physically configured, into various shapes, geometries, structures and configurations including, but not limited to, a film, fiber, rod, coil, corkscrew, hook, cone, pellet, tablet, tube e.g. smooth or fluted, disc, membrane, microparticle, nanoparticle, "biobullet" i.e. bullet shaped, seed i.e. bullet shaped or targeted seeds, as well as those described in the above identified products, patents and articles, including in some cases forming medical implants that have the same, similar or completely different functional characteristics compared to those functional characteristics of the medical devices described in the above identified products, patents and articles. The above-mentioned shapes, geometries, structures and configurations may contain additional features that will further enhance the desired application or use. For example, a polymer, compound and/or composition of the invention in the form of a rod, coil, or cone may have barbs that spring out upon insertion from a needle or cannula or when warmed to body temperature to reduce movement and/or expulsion. The shape, geometry, structure or configuration of a device, such as a medical implant, will vary depending upon the use of the device. For example, for treatment of a spinal cord injury or concussion to the brain, a polymer, compound and/or composition of the invention may be formed into a medical implant in the shape of a disc for placement under the dura or dura mater, or a solution, suspension, emulsion, cream, gel, ointment, or other adhesive formulation form for covering the spine, dura or other surgically exposed areas, film, sprayed or coated formulation. In another example, a polymer, compound and/or composition of the invention may be formed into a medical implant in the shape of a membrane or tube for use in the treatment of injury or damage to the

peripheral nervous system or a block of solid or foamed composition containing pathways drilled or otherwise formed to encourage nerve growth or bone growth. In another example, in the treatment of cancer, a polymer, compound and/or composition of the invention may be formed into a medical implant in the shape of a pellet, microparticle e.g. microsphere, nanoparticle e.g. nanosphere, rod, membrane, pin, cuff, disc, bullet, hook, rod or cone, with or without barbs, for insertion in a bone, joint, tumor excision site or other structures, or for insertion within the same and other structures. In the above instances, bioerosion of the medical implant would yield or generate an active agent. The invention also contemplates that the shape, geometry, structure or configuration of a medical implant of the invention may change depending on the mode of delivery or administration and may enhance the therapeutic effect of the medical implant. For example, a medical device of the invention may be in the form of a linear rod when inserted in needles and stored but may become coil-like or form a multiplicity of coils or corkscrew shapes as the medical implant is pushed out of the needle by a trochar. As a result of the change of the shape, geometry, structure or configuration of the medical implant, expulsion from the tumor or tumor excision site by hydraulic pressures or body movements may be prevented and as much mass of active ingredient may be delivered to a small region with as small a diameter needle as possible.

The polymers of the present invention may take the form of a shape memory polymer, which is a stimulus responsive material that may change its shape in response to outside stimuli. Usually this is a temperature-related effect. It depends on the morphology of the material in combination with various processing parameters. Thus, many materials of widely different polymeric chemistry may behave as shape memory. See, e.g. Lendlein and Kelch, on Shape Memory Polymers, Encyclopedia of Polymer Science and Technology, Ed III, Publ. J Wiley & Sons, New York (2003). The material may be programmed initially by deforming the sample, usually at an elevated transition temperature, and then cooled in a distorted form so that it remains in this temporary state. It will remain there a long time but on reheating to above the programming transition temperature it will revert to its natural undeformed state. Shape memory materials are all elastomers. They have a molecular structure consisting of network linked at certain net points either by physical or chemical cross-linking processes. The elastomer contains two types of polymer blocks whose phases are immiscible and have differing Tm or Tg values. Shape memory effects are usually recognized by tensile tests in a hot chamber over a range of transitions and seeing how the dimensions alter. The upper limit is the melting point of the highest Tm block. A cyclical regimen will show how well the polymer recovers its original shape. Examples of shape memory polymers are polyester-urethanes with hard and soft segments. A typical hard switching one is made from butane-1,4- diol and MDI with low Tg but crystalline polycaprolactone blocks. The Tm of the hard 4G-MDI block is the upper temperature limit. Another segmented polyether-urethane is the one from polyTHF and butane diol with MDI. Here, the molecular weight of the soft poly (THF) segment is important – if it is too high the recovery may suffer. Biodegradable shape memory polymers are possible based upon polycaprolactone diols capped with methacrylate groups and copolymerized with a low Tg amorphous vinyl component such as polybutyl acrylate. Other compositions may include block copolyester-ethers with hard segments such as polylactide, glycolide and soft segments such as polyTHF diol or caprolactone-diol. Polyanhydride links could be incorporated and if a phosgene route were used to make the polyanhydride it could also generate carbamoyl chlorides and urethane links at the same time form suitable amine precursors. The polymers of this invention achieve a broad range of tensile modulus anywhere between about 500, 1000, 5000, 10000, 50000, 100000, 300000 psi to about 500000, 600000, 850000, 1000000, 1200000, 1500000 psi and any combination of ranges therebetween.

The mode of delivery or administration of a medical device of the invention may vary depending upon the desired application and include those known in the art as well as those set forth herein. The thickness of the polymer, compound and/or composition as either the medical implant itself or as applied or coated onto a medical implant will vary depending upon one or more factors such as the physical and/or chemical characteristics of the polymer, compound and/or composition, the medical implant and/or the application or use. For example, a coronary artery stent may be formed from or applied or coated with a polymer, compound and/or composition of the invention to a thickness of about ≤30-50 μm while a vascular stent may be applied or coated with a polymer, compound and/or composition of the invention to a thickness of about ≤100 μm and a drug delivery device may be applied or coated with a polymer, compound and/or composition of the invention to a thickness of about ≤ 5 mm. In another example, round films/membranes for buccal (sublingual) administration (e.g., placement in lining of cheek, under the tongue) will have diameters of up to about 10 mm (1 cm) and a thickness of about 0.5-2.0 mm. In the present invention, a covering may be affixed to a medical device in several ways. In one embodiment, the covering may be placed on the outside of the medical device, and through the natural properties of the polymer (i.e., stickiness or adhesiveness), adhere to the device. In one embodiment, the covering may fit snugly, form-fitting, or loosely around the medical device, such that no adhesive is required to affix the covering to the medical device. In another embodiment, a covering of the invention may be affixed to the medical device by means of a biocompatible adhesive, the characteristics of which would be understood by one skilled in the art. In another embodiment of the invention, a covering may be affixed to a medical device by means of a device external to both the covering and the medical device. For example, the covering may be affixed to the medical device by means of an external clamp, retaining pin, or other such device commonly known in the art. External retaining devices used to affix a covering to a medical device may also be used to retain the shape of the covering. External retaining devices may retain the covering adjacent to the medical device by existing on the outside of the covering, on the inside of the covering (i.e., in between the covering and the medical device), or as a combination both outside and inside of the covering. In yet another embodiment, the covering may be affixed to the medical device by means of a fastener. Non-limiting examples of materials that may be used to make an external fixing device for a covering of the present invention include surgical steel, nylon, polyethylene, and combinations thereof. As a non-limiting example of the present invention, a medical device may be covered by a first covering in the form of a polymeric sheath, which is in turn covered by an external retaining device in the form of a semi-rigid or rigid sleeve. Such an external retaining device may be made of metal, plastic, a polymeric substance, or a combination thereof. Such an external retaining device may also be formed of, covered by, or impregnated with a polymer according to the present invention as described herein, or may be covered by or impregnated with an active agent that may be the same as or different than an active agent present in the first therapeutic device according to the present invention. An external retaining device may also contain a polymer that contains a functional group as described above. In another embodiment of the invention, an external retaining device that is formed from a polymer according to the present invention may contain at least one functional group and/or active agent in any of the forms as described above for a first covering.

In one embodiment, a cuff or sleeve comprising a polymer that generates an active agent, such as, e.g., an anti-inflammatory, an anti-infective, an antiseptic agent, or an anti-proliferative agent, is provided. Such a cuff may be made of the polymer entirely or made of an inert substance that is coated with the polymer. The cuff may adjoin or penetrate tissue layers to ensure delivery to the most

likely sites of infection. The simplest version of the embodiment would be to coat the surfaces of a suitable device with the polymer and thereby enable a slow release of active agent along its length within the moist and enzyme rich milieu of body tissue. In preferred embodiments, the medical device is coated with a polymer composition comprising a active agent including, but not limited to, an anti-inflammatory agent, an anti-infective agent, an antiseptic, and an anti-proliferative agent or drug. Polymers and compositions thereof with specific physical properties may be developed by one of skill in the art using the guidance given herein. In some preferred embodiments, a vascular medical device maybe further coated with a polymer that has lubricating qualities. A polymer, compound and/or composition of the invention may be combined or admixed with other ingredients prior to or while being formed into or coated onto a medical device or into a particular coating for a medical device. Examples of suitable additives include, but are not limited to, stabilizers, mechanical stabilizers, plasticizers, hardeners, emulsifiers, other polymers including other biocompatible and biodegradable polymers, e.g. biocompatible and biodegradable polyanhydrides as set forth in U.S.S.N. 09/917,231 and PCT Application US/01/23740, biocompatible and biodegradable polyazo compounds as set forth in U.S.S.N. 09/917,595 and PCT Application US/01/23748, biocompatible and biodegradable polyesters, polythioesters, and polyamides as set forth in U.S. Application No. 09/917,194 and PCT Application No. US/01/23747, the relevant portions of which are incorporated herein by reference in their entireties, radioopaque and/or radioisotopic materials e.g. boron, iodine, etc., suppositories, and other diagnostic or therapeutic agents or drugs. An added ingredient may enhance stability of the polymer, compound and/or composition itself, the medical implant itself and/or may enhance the diagnostic or therapeutic effect and/or may enhance or enable diagnostic activity. For example, if the added ingredient is a diagnostic or therapeutic agent or drug, bioerosion of the polymer would not only generate the active agent but would also release the diagnostic or therapeutic agent. In another example, by adding a radioopaque material, visualization of both the targeted area (e.g., tumor site, tumor) and the medical implant (e.g., catheter) would be enabled during and/or after (e.g., angioplasty, dental applications, joint injections, etc) insertion of the medical implant. In another example, the radioopaque material may also be used to control and/or enhance bioerosion of the medical implant and thereby control and/or enhance generation of the active agent by the generation of heat resulting from neutron capture. An added ingredient may also enhance the overall mechanical stability of the medical implant (e.g., carbon fibers). The type of additive used would vary and depend upon the desired property and application. In one embodiment, a medical device is coated with a therapeutic co-polymer of two or more monomers or more monomers that each independently have different linker groups. In other preferred embodiments, the medical device is coated with a therapeutic polymer composition that is comprised of at least two therapeutic polymers that are mixed after polymerization.

The first and second active agents may be the same or different active agents. In one embodiment, the first and second agents may both be incorporated into the backbone of the polymer or attached directly to the backbone, for example, through a linker or spacer molecule, or by direct or indirect chemical linkage to a chemical group attached to the backbone of the polymer; or the second active agent may be dispersed within the polymer matrix of the polymer or appended to the polymer, while the first active agent is incorporated into the backbone of the polymer or attached directly to the backbone, for example, through a linker or spacer molecule, or by direct or indirect chemical linkage to a chemical group attached to the backbone of the polymer; or the first and second active agent may be dispersed within the polymer matrix of the polymer or appended to the polymer. The polymer may also comprise additional active agents, such as a third active agent, a fourth active agent, a fifth active agent, and so on, where the additional active agents are released from the polymer upon hydrolysis, as

described herein. For example, the additional active agents may be incorporated into the backbone of the polymer or attached directly to the backbone, for example, through a linker or spacer molecule, or attached to the backbone by direct or indirect chemical linkage to a chemical group attached to the backbone of the polymer; or dispersed within the polymer matrix of the polymer or appended to the polymer as described herein, or otherwise annexed to or associated with the polymer such that the additional active agents dissociate from the polymer upon hydrolysis. In a preferred embodiment the medical device having at least one surface is provided, wherein the device comprises more than one polymer on all or a part of the surface, such as, e.g., a first polymer and a second polymer, which may be the same or different. The first polymer is capable of breaking down e.g. including, but not limited to, hydrolyzing or being enzymatically degraded, in the physiologic milieu to form a first active agent, and the second polymer is capable of breaking down in the physiologic milieu to form a second active agent. In one embodiment, the medical device comprises a polymer comprising at least one active agent, wherein the active agent or agents are incorporated into the polymer backbone. The first and second polymers may also comprise one or more additional active agents that are, e.g., incorporated, attached, appended or dispersed within the polymer, as described herein, or otherwise annexed to or associated with the polymer such that the additional active agents dissociate from the polymer upon hydrolysis. In one embodiment, the medical device has at least one surface, comprising more than one polymer on all or a part of the surface, such as, e.g., a first polymer and a second polymer. The polymers may be the same or different. The first polymer is capable of breaking down (e.g., including, but not limited to, hydrolyzing) in the physiologic milieu to form a first active agent, and the second polymer is capable of breaking down (e.g., including, but not limited to, hydrolyzing) in the physiologic milieu to form a second active agent, and the first and second active agents combine *in vivo* to form a third active agent. In one embodiment, the medical device comprises a polymer comprising at least one active agent, wherein the active agent or agents are incorporated into the polymer backbone. The first and second polymers may comprise one or more additional active agents that are, e.g., incorporated, attached, appended or dispersed within the polymer, as described herein, or otherwise annexed to or associated with the polymer such that the additional active agents dissociate from the polymer upon hydrolysis. For example, in one embodiment, the polymer is used as a coating for a device such as a stent that experiences expansion, contraction or torsion in application or use. In the case of vascular stents, the use of such a polymer coating could be used to reduce the incidence of inflammation and resulting hyperproliferation of cells that results in occlusion of the vessel (restenosis). In one embodiment, the linking group is a dicarboxlyic acid hydrocarbon chain with eight carbon atoms. In another embodiment the medical device is a stent. The stent may be any suitable stent, such as those described herein. Suitable stents include, for example, coronary vascular stents, peripheral vascular stents, urethral stents, biliary stents, stents used for supporting the lumen of other anatomical tubes, and stents used for other medical and veterinary treatments. In one embodiment, the medical device comprises a polymer comprising at least one active agent, wherein the active agent or agents are incorporated into the polymer backbone The stent may comprise additional polymers and/or additional active agents, such as, e.g., a second active agent, a third active agent, and so on, where the additional active agents are, e.g., incorporated, attached, appended or dispersed within the polymer, as described herein, or otherwise annexed to or associated with the polymer such that the additional active agents dissociate from the polymer upon hydrolysis. The stent may comprise active agents that combine *in vivo* to form a new active agent or agents. In a preferred embodiment an implantable stent is coated with the therapeutic polymer(s). The implantable stent may be made of many materials well known to those in the art, including but not limited to, electropolished 316L stainless steel and other metallic alloys as well as polymeric

materials. In preferred embodiments, the polymer coating that exhibits: 1) adequate wettability and adhesiveness to the surface of the stent to be coated, 2) adequate flexibility when crimped onto a balloon catheter, maneuvered into position, and then expanded in position in the body, 3) adequate hardness to avoid premature removal of the coating or portions thereof or pitting or other damage to the coating during implantation of the stent and thereafter (e.g., from handling, flow of blood or other body fluids, or movement of organs or the recipient's body), and 4) appropriate rates of degradation, enabling therapeutic drug levels to be maintained for predictable lengths of time without causing toxicity locally or systemically. For such a device used as a coronary, renal, or biliary stent, the preferred coating, or set of coatings, applied to the stent preferably has a thickness from about 100 nm to about 100 μm, and most preferably has a thickness from about 1 μm to about 30 μm. For stents used in other medical or veterinary applications, coatings or sets of coatings preferably have a thickness less than about 100 μm. In another embodiment, the therapeutic polymer is used as a coating(s) for an implantable orthopedic device, including hip, knee, shoulder, or elbow replacements, fixation devices, or devices for other orthopedic application. In the case of orthopedic and dental implants such a coating could be used to maintain bone strength or induce bone penetration of the device to stabilize it and/or to reduce pain and inflammation and/or to reduce infections. In one embodiment, the linking group is preferably a dicarboxylic acid hydrocarbon chain with four six, eight or ten carbon atoms.

In one embodiment, the medical devices are orthopedic implants, including hip, knee, and shoulder implants, and internal and external fixation devices and spinal implants. These orthopedic devices may be made of many kinds of materials well known to those in the art, including but not limited to, electropolished 316L stainless steel and other metallic alloys, inorganic ceramics including calcium phosphate and hydroxyapatite, cadaveric bone from humans and other animals, naturally-occurring and synthetic analogs of bone, biodegradable and non-degradable polymers (such as polymers of glycolic acid, lactic acid, and caprolactone, and copolymers thereof), and blends of the above materials. In one embodiment, the orthopedic implants are coated with a therapeutic polymer of the invention such that the polymer coating that exhibits: 1) adequate wettability and adhesiveness to the surfaces of the implant to be coated, such that the coating wets and penetrates into porous spaces percolating to the exposed surfaces of the device, 2) adequate flexibility when handled by the clinician, maneuvered into position, and then interfaced to tissue in the body, 3) adequate hardness to avoid premature removal of the coating or portions thereof or pitting or other damage to the coating during implantation and thereafter (e.g., from handling, flow of blood or other body fluids, or movement of organs or the recipient's body), and 4) appropriate rates of degradation, enabling therapeutic drug levels to be maintained for predictable lengths of time without causing toxicity locally or systemically. Compositions comprising a polymer may be used to coat orthopedic devices for fixation of bone fractures such as pins or screws, thereby decreasing the local inflammation and bone resorption associated with these devices. Films comprising an aromatic polyanhydride are also believed to be useful as orthopedic devices to enhance the healing process of bone fractures. A polymer may be coated or applied onto or formed into sutures, wound closures, stitches, staples and other related devices. In the case of sutures, staples and other devices such a coating could be used to reduce infections, pain and/or inflammation in the vicinity of the suture or staple. Fibers made of the present polymer(s) are useful as suture materials, and may be used in oral surgery to suture cleft palates. Use of a polymer that degrades to an active agent, such as a therapeutic salicylate, would enhance the regeneration of the tissue via the sutures while decreasing the pain and inflammation associated with the surgery via the degradation products. Films, membranes, pastes, gels, chips and microspheres comprising the polymer may also be used to decrease dental pain and promote healing

within a tooth, in the pulp chamber and root canal. Films or membranes comprising a polymer may also be used in guided bone or tissue regeneration. In one embodiment, the polymers, compounds and/or compositions of the invention may be formed into micronized particles or microparticles, or nanoparticles e.g. microspheres, nanospheres, nanocapsules and/or microcapsules. Microparticles of a polymer, compound and/or composition of the invention may be prepared by any means known in the art and may include one or more of the same or different polymer, compound and/or composition of the invention. For example, the microparticles may be prepared using an oil-in-water emulsion method whereby a polymer of the invention is dissolved in an organic solvent. The polymer solution is then added to a stirring solution of water and PVA (polyvinyl alcohol, which stabilizes the microparticle) resulting in the precipitation of the desired microparticles. Optionally, a homogenizer could be used. The solution is then allowed to settle, the solvent is decanted off the solution and the microparticles are then dried. The microparticles, e.g., microspheres, may be applied to the surface of a medical device before placement in the body. A sterile liquid may be used to coat the device to adhere such microspheres for minutes to weeks to enable uncoated medical devices to benefit from the same or similar therapeutic benefits as coated devices. In one embodiment, the nanoparticles or microparticles are typically but not necessarily less than about 10 nm or microns in diameter. In another oil-in-water emulsion method, the polymer solution is added to a solution of water and a surfactant such as PVA, which is stirred rapidly at high shear rates with, for example, a homogenizer or dispersator. After the addition of the polymer solution, the solvent is allowed to evaporate while stirring is continued. The resulting microparticles are recovered by decantation, filtration or centrifugation and dried. Microparticles of the invention may also be prepared by Southern Research Institute's (Southern Research Institute, Birmingham, AL) continuous microencapsulation process as set forth in U.S. Patent 5,407,609, which is incorporated herein by reference in its entirety, and is described in Figure 1, attached hereto. According to Southern Research Institute's continuous microencapsulation process described in Figure 1, proteins, peptides, small molecules, water-soluble drugs, hydrophobic drugs, and drugs encapsulated in lactide/glycolide polymers may be microencapsulated to sizes of about 1-250 µm, preferably <100 µm, more preferably, <10 µm with minimal exposure to polymer solvent, high encapsulation efficiency and good yields. As shown in Figure 1, a drug, polymer and polymer solvent dispersion is added to a mechanically agitated water/surfactant mixture to form an emulsion of microdroplets, which is then extracted with water to remove solvent and produce hardened microcapsules or microspheres for collection by centrifugation, filtration or the like.

The microparticles of the invention may be formed into various shapes and geometries e.g. spheres, and regular or irregular spheroid shapes. They may also be incorporated into various formulations or compositions e.g. gelatin capsule, liquid formulation, spray dry formulations, formulations for use with dry powder or aerosol inhalers, compressed tablet, topical gels, topical ointments, topical powder. As would be understood by one of skill in the art, the desired size of a microparticle of the invention will depend on the desired application and mode of delivery. Modes of administration or delivery of a microparticle and nanoparticle formulations of the invention include those set forth herein, including orally, by inhalation, by injection, and topically. The present invention contemplates the administration of microparticle and nanoparticle formulations that upon degradation or bioerosion may be delivered as is, or yield a smaller particle and/or active agent for the effective treatment of a targeted organ or tissue. The present invention also contemplates administration of one or more of the same or different microparticle or nanoparticle formulations of the invention having either all the same size or a mixture of two or more different sizes. By varying the size of the microparticle, the rate of bioerosion and/or the rate of generation of active drug and/or the location of active drug generation may be controlled. As a result, timed e.g. delayed and/or sustained generation of active drug may be achieved. For example, treatment of the inflamed wall of the colon, e.g. the treatment of inflammatory bowel disease, infections, and the like, may be achieved by oral administration of a microparticle of the invention containing as the active agent an anti-inflammatory drug. Such a microparticle of about 1 to about10 μm in size may be administered such that upon reaching the ileum region of the small intestine, the microparticle is about 0.1-1.0 μm in size, and about 0.01 to about 0.1 μm in size upon reaching the colon. See, for example Lamprecht et al., Abstracts/Journal of Controlled Release 72: 235-237 (2001). Once in the intestine, the microparticle may be physically entrapped by the villi and/or microvilli of the intestinal wall and/or by the mucous lining of the intestinal wall, thereby retarding expulsion, and prolonging gastrointestinal residence time and enabling timed sustained generation of the active agent in the proximity of the intestinal wall upon bioerosion of the polymer.

The microparticles of the invention may be of about 0.1, 1, 10, 20, 50 to about 60, 70, 80, 90 - 100 μm, preferably about 0.1 to about 10 μm, and any ranges therewithin. The microparticle of the invention may be administered orally such that blood levels of the microparticle enable perfusion of the active agent into the surrounding tissue upon bioerosion. In yet another example, oral administration of a microparticles of the invention of about 0.6 μm, preferably about 0.3 μm, more preferably about 0.1 μm, or any sizes therebetween, may be used to deliver an active drug through the intestine and eventually to the liver via the lymph system. See, for example Jani et al., Pharm. Pharmacol. 42: 821-826 (1990); Desai et al., Pharmaceutical Research 13 (12): 1838-1845 (1996). Microparticles of the invention of about 1 to about 50 μm may be applied topically or ocularly. Preferably, the microparticle is about 5 to about 20 μm. For subcutaneous or intramuscular injection, about 1-70 μm microparticle of the invention may be used. In one preferred embodiment, about 10 to about 70 μm microparticle of the invention is used for subcutaneous or intramuscular injection. In another preferred embodiment, an about ≤10 μm microparticle of the invention is used to create a product that feels smooth when applied to human skin. In another preferred embodiment, about 1 to about 3 μm microparticles of the invention are used for skin penetration. However, many other ranges of microparticle sizes may be used as well, as exemplified by Smart Particle™ and others (PowderJect Pharmaceuticals, U.K.; U.S. Patent Nos. 6,328,714, 6,053,889 and 6,013,050), in tissue, e.g. skin, mucosa, penetration applications which appear to rely more on shape and strength of the microparticle rather than size. The microparticles of the invention may also be used in an inhaled delivery, e.g. direct inhalation at a certain velocity, or by aerosol spray, to the lungs, including deep lungs, or pulmonary region. For example, a microparticle of the invention of about 0.5 to about 10 μm, preferably about 1-5 μm, more preferably about 1-3 μm, even more preferably about 1-2 μm may be formulated into an aerosol. For direct inhalation, about 0.5-6 μm, more preferably about 1-3 μm, microparticle may be used. See, for example AERx® System (Aradigm Corporation, Hayward, CA.) as well as those described in U.S. Patent Nos. 6,263,872, 6,131,570, 6,012,450, 5,957,124, 5,934,272, 5,910,301, 5,735,263, 5,694,919, 5,522,385, 5,509,404, and 5,507,277, and MicroDose DPI Inhaler (MicroDose Technologies Inc., Monmouth Junction, NJ) as well as those described in U.S. Patent Nos. 6,152,130, 6,142,146, 6,026,809, and 5,960,609. Microparticles of the invention of about ≤10μm may be used for intraarticular injections in the treatment of, for example, arthritis. A microparticle of the invention of about 0.1 to about 100 μm, preferably about 0.1 to about 10 μm, more preferably about 0.1-1 μm, may be admixed with a suppository, e.g. glycerin suppository. Nanoparticle formulations of this invention have diameters (average or range of size) about 2, 5, 10, 20, 50, 100 nm to about 150, 250, 350, 500, 700, 850 nm may be applied to therapeutic and prophylactic applications, such as healing of wounds and the like.

A polymer, compound and/or composition of the invention may also be formed into pellets, "biobullets", i.e. bullet shaped, or seeds, e.g. bullet-shaped seeds, for inclusion in an implantable and/or injectable bioerodable, hollow carrier **12** e.g. barrel, bullet, capsule, syringe or needle, as exemplified in Figures 2 and 3. Both animal and human applications are contemplated. Figure 2 illustrates several hollow needle-type carriers **12** for use in the invention. In one embodiment, hollow carriers **12** have a diameter ranging from about 0.5 to about 10 mm. Figure 3 illustrates placement of pellets, "biobullets," or seeds **10** of the invention inside the hollow cavity or chamber of a bioerodable needle-type carrier. According to the invention, one or more of the same or different pellet, "biobullet," or seed **10** of the invention may be placed inside the hollow carrier **12** or delivery device. The pellet, "biobullet" or seed **10** may be any size that will enable placement inside the hollow carrier **12**. The oral, injectable, implantable and topical formulations of the invention are suitable for uses in sub-cutaneous, intra-muscular, intradermal, and many other types of injections, site-specific injection by themselves or at site of other implant placement e.g. by other medical devices, in conjunction with other implanted materials such as bone cement and other adhesives, xenographs, collagen and other fillers, resorbable biomaterials, biodegradable and non-degradable biomaterials, in conjunction with excipients for oral and tablet formulation, in creams, ointments and topical formulations and solutions, suspensions and emulsions intended for application on external and internal surfaces of the body. Particularly preferred particle diameters include nanoparticle and microparticle ranges of about 10^{-9}, 10^{-8}, 10^{-7} to about 10^{-6}, 10^{-5} m. Useful formulations of the present polymers are types of particles: same as in uses by not with the topical application restrictions (i.e., creams, ointments, suspension, etc. but I would add encapsulation of particles (coated particles) and particles coated with our materials.

This invention also provides polymers in the form of a pellet, "biobullet," or seed **10** that upon bioerosion generate one or more agents. The invention also contemplates that the hollow carrier **12** may also be formed from a polymer, compound and/or composition of the invention such that upon bioerosion of the hollow carrier **12**, an active agent may be released and/or its contents, e.g. pellets, "biobullets" or seeds of the invention, may be released. In one preferred embodiment, pellets, "biobullets," or seeds **10** are made from a polymer of the invention containing salicylic acid admixed with follicle stimulating hormone (F.S.H.) and/or luteinizing hormone (L.H.) which are then placed in the hollow cavity or chamber of a bioerodable hollow carrier **12** or as part of a depot formulation (e.g., Lupron Depot®) for a timed release delivery of the hormones up to about 96 hours in order to stimulate ovulation. According to the invention, a pellet, "biobullet" or seed **10** of the invention and/or one or more hollow carriers **12** containing a pellet, "biobullet," or seed **10** of the invention may be placed in a delivery device, e.g. injector, gas-driven applicator. The delivery device may be further equipped with an axially slideable sleeve e.g. plunger, protrusions to prevent movement of the delivery device upon application e.g. chamfered protrusions, and handgrips. Examples of suitable carriers and/or delivery devices include, but are not limited to, those described in U.S. Patent Nos. 6,001,385, 5,989,214, 5,549,560; WO 96/13300, WO 96/09070, WO 93/23110, and EP 068053, each of which is herein incorporated by reference in its entirety. For example, U.S. Patent No. 5,989,214 and WO 96/13300 describe an apparatus for injecting the body of humans or animals with a pharmaceutical preparation, wherein the preparation is arranged in a rigid carrier, wherein the apparatus includes: a chamber into which the carrier may be transported; and a channel connecting onto the chamber for transporting the carrier into the body including fixation means for fixing the end of the channel relative to the skin of the body for injecting in order to prevent a movement of the channel in the direction perpendicularly of the axis of the barrel and where according to one embodiment the fixation means are formed by chamfered protrusions formed on the part adapted for

contact with the skin of the body and extending substantially in the direction of the axis of the channel. U.S. Patent No. 5,549,560, WO 93/23110, and EP 068053 describe a device for injecting humans and animals with a pharmaceutical preparation, wherein the preparation is held in a rigid carrier and the carrier is carried through the skin into the body by means of gas pressure, and wherein during carrying of a rigid carrier into the body by means of gas pressure the device with which the carrier is carried into the body is held against the body. U.S. Patent No. 5,549,560, WO 93/23110, and EP 068053 also describe a device for injecting animals or humans with a pharmaceutical preparation, wherein a chamber is present in which a carrier containing the pharmaceutical preparation may be placed, a barrel connecting onto this chamber and means for carrying the carrier by means of gas pressure through the barrel into the body for injecting, wherein means are present for blocking the use of the device when it is not pressed against a body. U.S. Patent No. 6,001,385 and WO 96/09070 describe "bullets" that are at least partly manufactured from substantially fully destructurized starch, particularly implants, suitable as vehicles for introducing active agents into the human or animal body in a transdermal manner. The present invention also relates to methods of using compositions comprising at least one active agent linked via the polymer backbone in any application wherein delivery of the active agent or agents is desired. Route of delivery is selected in accordance with drug being administered and the condition being treated. In one embodiment, the polymers decompose harmlessly while delivering a selected low molecular weight drug at the site of implantation within a known time period. Another aspect of the present invention provides a method for site-specific or systemic drug delivery by implanting in the body of a patient in need thereof an implantable drug delivery device containing a therapeutically effective amount of a biologically or pharmaceutically active compound in combination with polymer of the present invention. In one embodiment, the polymers of the invention may be particularly useful as a controlled release source for an active agent, or as a medium for the localized delivery of an active agent or agents to a selected site. For example, the polymers of the invention may be used for the localized delivery of a therapeutic agent to a selected site within the body of a human patient (i.e. within or near a tumor), where the degradation of the polymer provides localized, controlled, release of the therapeutic agent. In one embodiment, a method for delivering an active agent to a patient is provided. The method comprises providing a medical device having at least one surface, comprising a first polymer on all or a portion of the surface, wherein the polymer is capable of breaking down (e.g., including, but not limited to, hydrolyzing) in the physiologic milieu to form a first active agent, and administering the device to the patient such that the first active agent is delivered to the patient. The device may comprise additional polymers and/or additional active agents, such as, e.g., a second active agent, a third active agent, and so on, where the additional active agents are, e.g., incorporated, attached, appended or dispersed within the polymer, as described herein, or otherwise annexed to or associated with the polymer such that the additional active agents dissociate from the polymer upon hydrolysis and are delivered to the patient. The device may comprise active agents that combine *in vivo* to form a new active agent or agents that is delivered to the patient. The active agent or agents may be delivered to any suitable site or sites in a patient, such as, for example, the circulatory system (e.g., a vein or an artery), a tissue, an organ (e.g., lung, liver, spleen, kidneys, brain, eye, heart, muscle, and the like), a bone, cartilage, connective tissue, epithelium, endothelium, nerves, a tumor, or any other site suitable for delivery of an active agent or agents.

Suitable sites will typically be sites that are or will be in need of treatment with an active agent or agents, such as, e.g., an injured site or a site that may become injured, for example, due to a disease, a medical condition, or during or after a medical procedure, such as, e.g., a balloon angioplasty and/or implantation of a medical device. In one embodiment, a method for delivering an active agent to an interior surface of a vein or artery is provided. The method comprises providing a medical device having at least one surface, comprising a first polymer on all or a portion of the surface, wherein the polymer is capable of breaking down (e.g., including, but not limited to, hydrolyzing) in the physiologic milieu to form a first active agent, and positioning the medical device at or near the interior surface of the vein or artery such that the first active agent dissociates upon hydrolysis and is delivered to the interior surface of the vein or artery. The device may comprise additional polymers and/or additional active agents, such as, e.g., a second active agent, a third active agent, and so on, where the additional active agents are, e.g., incorporated, attached, appended or dispersed within the polymer, as described herein, or otherwise annexed to or associated with the polymer such that the additional active agents dissociate from the polymer upon hydrolysis and are delivered to the interior surface of the vein or artery. The device may comprise active agents that combine in vivo to form a new active agent or agents that are delivered to the interior surface of the vein or artery. In one embodiment, the method prevents, reduces, and/or inhibits the development of restenosis in the blood vessel. Restenosis may be defined as, for example, the narrowing of the vessel to about 80%, about 70%, about 60%, about 50%, about 40%, about 30%, about 20%, about 10% or less, of the diameter of the vessel after removal of any blockages from the vessel and the placement of the device into the vessel. The compositions, devices and methods of the present invention are useful for treating a wide array of diseases and conditions, including, for example, those set forth below and/or otherwise described herein. In cardiology, such compositions, devices and methods may be used, for example, to develop coatings for stents, sutures and pacemakers, or other devices used in cardiology as otherwise referenced herein. In ophthalmology, such compositions, devices and methods may be used, e.g., to develop a lens replacement for cataracts with a translucent polymer; for a direct injection of microspheres into the eye to provide a depot of anti-inflammatory therapy; or for the treatment of glaucoma. In otolaryngology, such compositions, devices and methods may be used, e.g., to develop antibiotics for otic administration, e.g. amoxicillin microspheres or nanospheres; for reconstructive surgery, e.g. bone restructuring; as a treatment for tuberomandibular joint (TMJ) pain by direct injection; as a treatment of chronic sinusitis by injection of microspheres; or for compositions delivered via inhalers, e.g. dry powders or admixed with non-CFC propellants. In bone and orthopedic applications, such compositions, devices and methods may be used, e.g., to develop orthopedic injections of inventive compositions; for bone implants; for the prevention of bone erosion; for wound healing by inhibiting osteoclasts and preventing spurious bone growth; as bone putty; for spinal cage bone pins (e.g., mixture of inventive polymers with hydroxyapatite fillers and other fillers); as a coating for orthopedic implants to decrease pain, inflammation, bone erosion and infections; as combinations of poly-NSAIDS plus poly-antibiotics to treat osteomyelitis or other bone infections by direct injection into the marrow; for the treatment of bone cancer with antiproliferatives; for the treatment of trauma; as prosthetic devices and coatings therefore; or other devices used in bone and orthopedic applications as otherwise referenced herein.

In neurology, such compositions, devices and methods may be used, e.g., to develop microspheres injections for injection into the cerebral spinal fluid. In oncology, such compositions, devices and methods may be used, e.g., to treat any suitable cancer, such as, e.g., liver cancer, ovarian cancer, prostate cancer, and breast cancer; for delivery to any surgical site where cancer is removed and there exists a concern that not all cancer cells were removed; or to develop compositions of poly-antiproliferatives sprinkled into the peritoneum, which slowly erode and circulate through the lymphatic system where the primary metastases congregate. In dentistry, such compositions, devices and methods may be used, e.g., to develop alveolar bridges, tooth implants, patches for treating long-term pain, microspheres to treat or prevent dry socket, chips and wafers, chewing gum, dental floss and microspheres coatings on toothbrushes; and for the prevention of bone erosion. In gastroenterology, such compositions, devices and methods may be used, e.g., for oral administration of inventive polymers with antacids to treat ulcers, heartburn and other acid-related diseases; for the treatment of irritable bowel syndrome with inventive compositions having a particular particle size; or for use of the compositions (e.g., a poly-NSAID) to prevent or treat inflammation at a colostomy sinus. In obstetrics and gynecology, such compositions, devices and methods may be used, e.g., for the prevention of toxic shock syndrome by using the inventive compositions in fibers of tampons; for the treatment of yeast infections; for the treatment of chlamydia infections; as suppositories; as a cervical ring to treat or prevent cramps or premenstrual syndrome; and as surgical meshes and coatings to treat hernias. Surgical applications of such compositions, devices and methods include, e.g., as coatings for bladder catheters; as coatings for indwelling catheters; as coatings for biosensors, particularly the leads, to prevent scarring and granulomas and to avoid signal interference and increase battery life; as compositions as surgical adhesives; as microspheres sprinkled into any surgical field to prevent adhesions; and for subdural barriers or films to prevent swelling and inflammation. The compositions, devices and methods may also be used in wound healing applications, including, e.g., as sutures, surgical meshes, bandages, and other mechanical wound closure products or coatings thereof. The compositions may be also be in the form of microparticles, e.g. microspheres, microplatelets or other microstructures) as a powder or pellets to be applied locally, e.g. sprinkling, to the affected area. In dermatology, such compositions, devices and methods may be used, e.g. to develop sunscreens; insect repellants (admixed or polymerized compounds e.g., DEET; Merck IR 3535; citronella); bandages; as microspheres in patches to deliver systemically active drugs; for the treatment of psoriasis (poly-methotrexate optionally combined with poly-NSAID); for the treatment of seborrhea; and for the treatment of dandruff. Polymers of the present invention may also be incorporated into oral formulations and into products such as skin moisturizers, cleansers, pads, plasters, lotions, creams, gels, ointments, solutions, shampoos, tanning products and lipsticks for topical application.

Formulations

The polymers of the invention may be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e., orally, rectally, or parenterally, by intravenous, intramuscular, intraperitoneal, intraspinal, intracranial, topical, ocular, pulmonary or subcutaneous routes. For some routes of administration, the polymer may conveniently be formulated as micronized particles. Thus, the present compounds may be systemically administered orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilatable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations preferably contain at least 0.1% of polymer by weight. The percentage of agent or polymer in the compositions and preparations may, of course, be varied and may conveniently be about 0.1, 1, 25, 10, 30, 45 to about 50, 60, 75, 80wt%, and any ranges defined by their combination, and of a given unit dosage form. The amount of polymer in such therapeutically useful compositions is such that an effective dosage level will be obtained. The tablets, troches, pills, capsules, and the like may also comprise binders such as gum tragacanth, acacia, corn starch, gelatin or others; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The polymer may also be administered subcutaneously, intramuscularly, intravenously, intraspinally, intracranially, intrauterally, rectally, intraperitoneally, and into and around any applicable body cavity, wound and surgical site by infusion or injection. Solutions of the polymer may be prepared with a suitable solvent such as an alcohol, optionally mixed with a nontoxic surfactant. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms. The pharmaceutical dosage forms suitable for injection or infusion may include sterile solutions or dispersions or sterile powders comprising the polymer containing the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle may be a solvent or liquid dispersion medium comprising, for example, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity may be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms may be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions may be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin. Sterile injectable solutions are prepared by incorporating the polymer in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present polymers may be applied in pure form. However, it will generally be desirable to administer them as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid. Examples of useful dermatological compositions which may be used to deliver the polymers of the invention to the skin are known to the art. See, for example U.S. Patent Nos. 4,608,392; 4,992,478; 4,559,157; 4,820,508. Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include alcohols or glycols or alcohol/glycol blends, in which the present compounds may be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents may be added to optimize the properties for a given use. The resultant liquid compositions may be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers. Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials may also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Doses

Useful doses of the polymers may be determined using techniques known in the art, such as, e.g., by comparing their *in vitro* activity with the *in vivo* activity of the therapeutic agent in animal models. Methods for the extrapolation of effective doses in mice, and other animals, to humans are known to the art; for example, see U.S. Patent No. 4,938,949. Additionally, useful doses may be determined by measuring the rate of hydrolysis or enzymatic degradation for a given polymer under various physiological conditions. The amount of a polymer required for use in treatment will vary not only with the particular polymer selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician, and is easily determinable by one of ordinary skill in the art. The quantity of polymeric drug to be administered to a host that is effective for the selected use may be readily determined by those of ordinary skill in the art without undue experimentation. The quantity essentially corresponds stoichiometrically to the amount of drug which is known to produce an effective treatment for the selected use. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations. The total amount of active agent released will vary depending on the particular active agent and treatment protocol involved, as is easily determined by one ordinarily skilled in the art. The amount of active agent released will typically be from about 0.1 μg to about 10 g, preferably from about 1 μg to about 100 mg, more preferably from about 10 μg to about 10 mg, more preferably from about 50 μg to about 1 mg. Preferably, the polymers are formulated to provide local release of an effective amount of an active agent or agent over a period of at least about 2, about 5, about 10, about 20, or about 40 days. The compositions may also preferably be formulated to provide local release of an effective amount of the agent over a period of up to about 3 months, about 6 months, about 1 year, or about 2 years.

The active agent may be released from the polymer at any rate suitable for appropriate delivery of the active agent to the patient. In one embodiment, the active agent is released at a rate from about 0.01 μg per day to about 100 mg per day, from about 1 μg per day to about 10 mg per day, or from about 10 μg per day to about 1 mg per day. It will be appreciated that the greater the potency of the coating, the better with regard to minimizing the space required for the administered product, the potential cost of the product, the ease of manufacturing the product, and the potential impact on other desired properties of the medical implant. The polymers of the present invention may be characterized by techniques known in the art. Degradation and drug release profiles of the polymer drug delivery systems of the present invention may also be determined routinely. The range of therapeutically effective dosages, that is, the dosage levels necessary to achieve the desired result, of a microparticle of the invention will be influenced by the route of administration, the therapeutic objectives, and the condition of the patient. As such, a polymer of the invention may be administered as a single daily dose, several times daily, every other day, weekly, etc. depending on the dosage requirements. Individual determinations will need to be made to identify the optimal dosage required.

Co-Polymers and Blends of Polymers

The therapeutic polymers and compositions thereof used in some applications, such as for coating implantable medical and veterinary devices, including stents and orthopedic implants, may require greater elasticity or flexibility while retaining sufficient hardness and adhesiveness to remain intact on the device as the device is handled or otherwise manipulated by the clinician or surgeon or within the body of the patient, such as, e.g., when the device interacts (e.g., mechanically and chemically) with the surrounding tissue or fluid or luminal wall, or, in the case of a stent, with the intraluminal wall of a vessel in which the vessel and stent experience pulsatile motion due to the pulsatile nature of blood flow and the contraction of the vessel wall by the associated smooth muscle. To provide desired physical properties, including mechanical strength, modulus, and elongation without failure, it is possible to create coating comprised of a co-polymer of two or more monomers used to create the two or more polymers that have physical properties and other performance characteristics bracketing those properties and characteristics desired. In one embodiment, copolymers of similarly sized or "sequential" linkers, i.e. adipic acid (C6) and suberic acid (C8) are made in order to "fine tune" the physical properties of the polymer to a state between the two available linkers. However, "non-sequential" co-polymers are also contemplated, for example a co-polymer containing adipic acid (C6) and sebacic acid (C10) linkers. Additionally, co-polymers comprising three or more linker group moieties are also contemplated. In one embodiment, the co-polymer is formed of monomers of salicylic acid and adipic acid, and salicylic acid and suberic acid, at about 50% or more mole percent of the co-polymer is the monomer salicylic acid and adipic acid respectively. However, proportions of any of the agent monomers may be employed in the polymers of the invention, such as about 5, 10, 20, 30, 40, 50 to about 60, 70, 80, 90, 95, 99 wt%. Alternatively or in combination with one or more of the co-polymers described above, it is possible to create a physical blend of two or more polymers or co-polymers in which the individual polymers or co-polymers blended each have a set of physical properties and performance characteristics that meet or exceed requirements for a coating for the specified implantable medical or veterinary device and its application but may have one or more physical properties and performance characteristics that are insufficient for that device and its application, such that the combination of properties and characteristics provided by the blend meet or exceed the required properties and characteristics needed for the device and its application.

These blends may be of polymers that are miscible or immiscible in each other. For example, it is possible to make a co-polymer or blend of polymers or co-polymers in which one monomer in the co-polymer or one polymer or co-polymer in the blend has a hardness that exceeds the requirements for the coating for the device and its application but a flexibility insufficient and another monomer in the co-polymer or another polymer or co-polymer in the blend that has a flexibility sufficient but a hardness insufficient for the device and its application. The physical properties and performance characteristics of the copolymer may be fine tuned further by selecting the percentage of each monomer in the copolymer or the percentage of each polymer or co-polymer in the blend towards the combination of monomers or polymers or co-polymers that produce a coating that has physical properties and performance characteristics closer to the desired set. In an exemplary embodiment, a polymer comprising salicylic acid or a derivative of salicylic acid, such as diflunisal, and linkers of dicarboxylic acids in which the pair of carboxylic acids within the diacid are separated by a linear alkyl chain, is coated on a stent or other device experiencing expansion, contraction, or torsion in application or use. A coating comprising a polymer in which the alkyl chain comprises six atoms of carbon (known as adipic acid) may crack or craze upon change in dimensions, e.g. expansion for a stent, whereas a coating comprising a polymer in which the alkyl chain comprises eight atoms of carbon (known as suberic acid) may be excessively tacky or otherwise adhere to the materials used in handling and implantation, e.g. the balloon used for expansion of the stent. For such applications, in the absence of an admixed drug or other additive that alters the physical properties and performance characteristics in a predictable and repeatable manner, a suitable coating may comprise, for example, a polymer of salicylic acid and suberic acid or a copolymer of monomers of salicylic acid and dicarboxylic acid or a physical blend of polymers or co-polymers of salicylic acid and dicarboxylic acid that approximate the tradeoffs in physical properties and performance characteristics, including hardness, tackiness, and flexibility, of polymers created with a linker of suberic acid. In another exemplary embodiment, a polymer comprising salicylic acid or a derivative of salicylic acid, such as diflunisal, and linkers of dicarboxylic acids with linear alkyl chains, and is coated on an orthopedic implant for use as a hip, knee, shoulder, elbow replacement, a fixation device, or another orthopedic application. In the absence of an admixed drug or other additive that alters the physical properties and performance characteristics in a predictable and repeatable manner, a suitable coating may comprise, e.g., a polymer of salicylic acid and a dicarboxylic acid linker with four, six, eight or ten carbon atoms in the linear alkyl chain (known as succinic and adipic acids, respectively) or a copolymer of monomers of salicylic acid and dicarboxylic acid or a physical blend of polymers or co-polymers of salicylic acid and dicarboxylic acid that approximate the tradeoffs in physical properties and performance characteristics, including hardness, tackiness, and flexibility, of polymers created with a linker of succinic or adipic acids.

Combination Therapies

The polymers of the invention are also useful for administering a combination of therapeutic agents to an animal. Such a combination therapy may be carried out in the following ways: 1) a second therapeutic agent may be dispersed within the polymer matrix of a polymer of the invention, and may be released upon degradation of the polymer; 2) a second therapeutic agent may be appended to a polymer of the invention (i.e. not in the backbone of the polymer) with bonds that hydrolyze to release the second therapeutic agent under physiological conditions; 3) the polymer of the invention may incorporate two therapeutic agents into the polymer backbone; or 4) two polymers of the invention, each with a different therapeutic agent may be administered together (or within a short period of time). Of course, more than one therapeutic agent may be used in each of the above cases. Thus, the invention also provides a medical device comprising a polymer that hydrolyzes to form a first active agent and a second active agent that is dispersed within the polymer matrix of a polymer of the invention. The invention also provides a medical device comprising a polymer that hydrolyzes to form a first active agent having a second active agent appended to the polymer (e.g. with bonds that will hydrolyze to release the second therapeutic agent under physiological conditions).

The polymers of the invention may also be administered in combination with other active agents that are effective to treat a given condition to provide a combination therapy. Thus, the invention also provides a method for treating a disease in a mammal comprising administering an effective amount of a combination of a polymer of the invention and another therapeutic agent. The invention also provides a pharmaceutical composition comprising a polymer of the invention, another therapeutic agent, and a pharmaceutically acceptable carrier. Suitable drug combinations for incorporation into the polymers or the compositions of the invention include for example, a first active agent that is classified as a non-steroidal anti-inflammatory drug (NSAID), such as, e.g., salicylic acid or diflunisal, combined with a second active agent classified as an anti-cancer and/or anti-neoplastic agent, e.g. paclitaxel or methotrexate, or as an immunosuppressive, e.g. rapamycin. Preferred drug combinations for incorporation into the polymers or the compositions of the invention include amoxicillin/clavulanic acid; and imipenem cilastatin, among others.

<u>Admixing Component Materials</u>

The formation of a composite of two or more materials results in a new material that may have physical properties and performance characteristics substantially different from any of the individual component materials comprising the new material. In the case of polymers, these altered physical properties may include an increase or decrease in glass transition temperature, tensile or shear moduli, effective viscosity, yield strength and elongation, elongation at failure, tackiness or adhesiveness, hardness, color, rate of thermal or biological breakdown, surface texture, or wettability by water or other fluid. For example, the mechanical properties of bone, a composite of inorganic calcium phosphates and organic collagen molecules, are distinct from the mechanical properties of either calcium phosphates or collagen alone. In one embodiment, a polymer of the invention is admixed with an anti-proliferative agent, such sirolimus, everolimus or paclitaxel, or other material or agent, such as specific RNA and DNA sequences and their chemical mimics or derivatives, calcium phosphate, hydroxyapatite, an antibiotic, an immunosuppressive agent, or another agent. These added compounds may alter the mechanical properties of the polymer (e.g., by modifying the degradation rate, the tensile modulus, the yield strength, and/or the elongation at which failure of the material occurs). Coatings made from the therapeutic polymer will also exhibit the altered mechanical properties. The extent to which the admixture of one or more drugs or other therapeutic agents changes the physical properties and performance characteristics of the coating will depend on the amount or concentration of each of the drugs or agents, with a trend that increasing the amount or concentration of a drug or agent is expected to increase, if at any changes occurs at all, one or more of these properties or characteristics. In practice, coatings with about 0.1, 1, 3, 5, 10 wt% or more to about15, 20, 30, 35, 40, 45wt% admixed drug or agent may be achieved by blending the admixed compound into the polymer prior to coating or by first applying the polymer as a coating and then absorbing the compound to be admixed into the coating by exposing the coating to a solution with the compound. In an exemplary embodiment, a coating of a polymer with an admixed drug, applied on an expandable stent, comprises a dicarboxylic acid with more than six carbon atoms in the linear alkyl chain, or a co-polymer or physical blend of polymers or co-polymers that approximate the physical properties and performance characteristics of the polymer with a linker with more than six carbon atoms in the linear alkyl chain, such that these polymers approximate the physical properties and performance characteristics of a polymer with a linker of suberic acid (C8). In another exemplary embodiment, a coating of a polymer with an admixed drug, applied on an orthopedic implant, comprises a dicarboxylic acid with more than four carbon atoms in the linear alkyl chain, or a co-polymer or physical blend of polymers or co-polymers that approximate the physical properties and performance characteristics of the polymer with a linker with more than four carbon atoms in the linear alkyl chain, such these polymers approximate the physical properties and performance characteristics of a polymer with a linker of succinic (C4) or adipic (6C) acid. In some embodiments, compositions comprising polymers may have optimum physical and chemical properties derived by blending compounds into the polymer that decrease or increase the rate of penetration of water and/or enzymes into the polymer matrix and, thereby, decrease or increase the rate of breakdown of the polymer, thereby modulating the duration of generation of drug from the components of the polymer backbone and/or the release of admixed drug or agent. In addition, qualities such as shelf life, e.g. stability in the presence of elevated temperatures, humidities, or electromagnetic radiation, rates of depolymerization, e.g. by hydrolysis or proteolytic activity, or oxidation, and rates of hydration may be varied by adding antioxidants or lipophilic molecules to reduce oxidation or hydration of the polymer blend, respectively. In some cases, the qualities of the admixed drug or agent may influence the physical or chemical properties, including shelf life, tolerance to sterilization methods, or degradation rate of the final product. For example, the admixed drug or agent may extend the shelf

life, increase the types and/or dosages of sterilant that may be applied without changing other properties of the material, or decrease or increase the degradation rate of the final product.

Layering Coatings of Polymers

The polymers of the invention may be layered onto devices with other polymers of the invention, or other polymers in general, to form coatings with desirable properties. The therapeutic polymers may be structured and/or layered as a coating with one or more additional coatings that may or may not be biodegradable (i.e., degradable by hydrolysis or enzymatic/proteolytic activity when placed in contact or exposed to body tissues or fluids). The additional coatings may contain the same polymerized active compound, a different polymerized active compound, no polymerized active compound, or one or more admixed drugs or agents. This structuring may be in the form of a layer of a coating on the exposed surface of the coating of the therapeutic polymer such that this coating lies between the polymerized active compound, and the body tissues and/or fluids following implantation. Alternatively, a second polymer or smaller molecular-weight species may be physically blended with the therapeutic polymer, and a series of layered coatings of therapeutic polymer compositions that have different chemical compositions and/or physical (e.g., mechanical) properties. Several, but not all, of the possible structuring of layers are depicted in Figure 1.

In some embodiments of the invention, layering permits refinement of the rate or duration of generation, release, or elution of active agents over time, including the possibility of having one or more outer coatings with higher or lower permeability to modulate the breakdown of one or more inner coatings and thereby result in a more constant release of active agent over particular periods of time. In embodiments in which one or more outer coatings are biodegradable, the breakdown and resulting increase in permeability of these outer coatings may compensate for a rate of generation (by breakdown of the polymer) or release of an active agent that varies with time by increasing the rate of permeation of the active agent from the inner coating through the outer coatings. Such embodiments may be used to create a rate of delivery of drug from the coatings on the device that vary less temporally (i.e., are more closely more zero-order) and that may be adjusted based on the preferred shape and, therefore, surface area of the device and changes in surface area that occur as the coatings erode. Multiple layers of polymers generating, eluting, or releasing inert and active products upon breakdown may be designed for specific applications, including those applications in which one class or member of a class of agents is to be generated, eluted, or released from the coating before a second class or a second member of the first class of agents is generated, eluted, or released from the coating. An example of such a layered coating, as depicted in Figure 1c, is a coating in which an anti-inflammatory agent (e.g., from the class of NSAIDs) is generated, eluted, or released from the coating 30 substantially before an anti-proliferative agent is generated, eluted, or released from the coating 10. Such types of layered coatings 40 enable tuning of the rate of generation, elution, or release of drugs from the coating over time, such that a near constant, gradually increasing, gradually decreasing, or a combination thereof amount of drug most appropriate for treatment of tissues in the vicinity of the device may be delivered to these tissues. In some embodiments of the invention, one or more inert polymer coatings may applied as one or more top coats on one or more coatings of one or more polymers, including coatings with admixed drugs or other agents. Top coating may be applied to increase the hardness and/or or lubricity of the coating and, thereby, the device during insertion or use. Additionally, top coating may be applied to vary, e.g. increase or decrease, the rate of hydration or enzyme penetration and, thereby, vary, e.g. increase or decrease, the rate of generation of the drug from the polymer backbone or release of an admixed drug or other agent from the underlying coating. Finally, top coatings may be applied to increase the shelf life of the final product by limiting the penetration of water or oxygen into the underlying therapeutic polymer coating. In preferred embodiments, the top coatings will be biodegradable. The polymers of this invention achieve degreess of hardness suitable for a variety of applications. Generally, the hardness, based on a Shore hardness range, comprises about 24, 26, 28, 35, 45, 55 to about, 60 , 70, 80, 95, 101. Different applications call for different degrees of polymer hardness that are achievable in their application to the devices of the invention as required.

One preferred rate of drug delivery may be achieved by using multiple layers of polymer. In some cases different concentrations of the same admixed drug may be used in each layer or different copolymers having different rates of drug generation and/or polymers with different breakdown rates for release of admixed drugs or agents may be used in each layer, thereby achieving a predictable and repeatable timing of delivery of one or more bioactive agents. Such layering effects may be enhanced by a combination of layers of inert polymer and/or layers with inert polymer with admixed drug or agents and/or layers with therapeutic polymers and admixed drugs or agents and/or layers with only therapeutic polymers. In an exemplary embodiment, an outer coating that would provide an initially high dose of anti-inflammatory agent that is followed by the release or generation of an anti-proliferative agent from underlying layers. In one embodiment, a medical device is coated with more than one layer of polymer, where at least one layer is the therapeutic polymer of the invention. The polymers include but are not limited to "inert" polymers that do not breakdown or breakdown into non-therapeutic agents. One or more coatings or layers of an inert or therapeutic polymers may be used to advantage with the therapeutic polymers of the invention to regulate the release of active agents released from or generated by therapeutic polymer underlying the coating or layer of polymer. In more preferred embodiments, the active agent(s) is predictably and repeated released over time. For example, the active agent may be released from the set of coatings at a steadily increasing or decreasing rate, or at a nearly constant rate over time. In other more preferred embodiments, the outer layer(s) of polymer slow or prevent the penetration of water and/or enzymes to the inner layer(s) of therapeutic polymer. These embodiments are useful to lengthen the shelf-life of the medical device, and/or to regulate the release or generation of the active agent in underlying layers. In most preferred embodiments, the layer(s) of therapeutic polymer on the medical device are further coated with a layer of polymer which is polylactic acid, a polymerized form of amino acids, a polymerized form of fatty acid metabolites, and derivatives and/or combinations of any of these.

Both types of polymers have been made with several different linker molecules that modulate their physical properties and NSAID generation profiles (see Figure 5 and Table 2 for examples).

Table 2: Straight-Chain Dicarboxylic Acid Linkers

NAME	CHEMICAL FORMULA	COMMENTS
Succinic Acid	$HO_2C(CH_2)_2CO_2H$	Rat Oral LD_{50} = 8,530 mg/kg
Adipic Acid	$HO_2C(CH_2)_4CO_2H$	Rat Oral LD_{50} = 5,050 mg/kg
Suberic Acid	$HO_2C(CH_2)_6CO_2H$	
Sebacic Acid	$HO_2C(CH_2)_8CO_2H$	Rat Oral LD_{50} = 14,470 mg/kg
Dodecanoic Acid	$HO_2C(CH_2)_{10}CO_2H$	Marketed as dietary supplement
Tetradecanoic Acid	$HO_2C(CH_2)_{12}CO_2H$	In Foods (e.g., butter)
Hexanedecanoic Acid	$HO_2C(CH_2)_{14}CO_2H$	-

All of these molecules are produced enzymatically by fatty acid synthase and are routinely present in the body (and in foods) in varying amounts. Available data indicate that they are highly non-toxic after oral administration. In fact, one form is currently being marketed in the U.S. as a dietary supplement. While many effects of these molecules administered directly to tissues are not fully known, they are likely to be innocuous. As noted above one of these molecules, sebacic acid, was approved by the FDA as a linker in a wafer for insertion into brain tissue (GLIADEL®, Guilford Pharmaceuticals).

Polymer Production and Handling

The polymers of this invention, such as the polySA and polyDF being described for exemplary purpose only, may be produced by a number of methods. In each case, the polymers are produced by chemically connecting repeating monomers ("-mers"). Each repeating unit contains two drug molecules connected via ester bonds to one linker molecule; the drug molecules are connected via anhydride bonds. In the standard "melt condensation" approach used to prepare the p[olymer of this invention, e.g. polyAspirin, the monomers were dissolved in a solvent and stirred for several hours at relatively high temperatures. The inventors produced polymers such as polySA and polyDF polymers by this method, with molecular weights ranging from about 30,000 to about 90,000 and poly-dispersities, a measure of polymer homogeneity, of about 1.5 to about 3.0. Other methods permit the preparation of polymers in higher yields, as well as of higher MWs and greater uniformity than prior methods permitted. By definition, all biodegradable polymers are designed to degrade and release its agent(s) over a period of time. Unlike other poly(anhydride-ester) polymers reported in the literature, the present polymers are highly soluble in common industrial solvents, and are relatively stable (as measured by loss of molecular weight) both in bulk and in solution. The desirable "bulk stability", or molecular weight stability of the polymers at room temperature is generally about 1 week, 1 month, 6 months to about 8 months, 1 year, 2 years, although longer periods of stability may be attained as well. As with most other drugs the stability of the polymers of this invention is enhanced by storage under dry conditions and at low temperatures e.g. -20°C. However, even under unprotected ambient conditions, polymers such as polyNSAIDs are stable for weeks, and storage-related changes in molecular weight do not significantly affect polymer performance for drug delivery.

Effect of Linker Chain length on Glass Transition Temperature and Mechanical Properties

Glass transition temperature (T_g) is a key parameter of polymers that significantly influences their mechanical, physical chemical and handling properties. As shown in Figure 6, a polySA polymer with a six-carbon linker molecule has a T_g = 44°C, and is relatively hard at room temperature. Increasing the carbon-chain length lowers T_g in a linear manner, so that polySA produced with a 12-carbon linker molecule has a T_g=8°C, which results in a rubbery, elastic material at room temperature. A similar profile is seen with polyDF polymers, noting that for a specific linker chain length, a much higher T_g is measured relative to the same linker in the polySA polymers. As summarized in Table 3a shown below, tensile modulus (another index of rigidity) also increased with decreasing linker chain length, while for a specific linker, rigidity decreased as temperature was increased from 25°C to body temperature (37°C).

As shown in Table 3a, in one of the embodiments of the invention, the Tg of the polymer was seen to increase with increased length of the carbon chain. In another embodiment shown in Table 3b the Tg may increase until certain number of carbons in the chain, e.g. glutaric acid vs. adipic acid. A linker of a very short carbon chain, e.g. C < about 5, provides less of a chance for cross-linking in any of the generally known sythetic methods, e.g. melt polymerization variations, probably due to steric

hindrance and the polymer produced may have a lower Tg (e.g. about 58 °C) than when the linker has a longer chain that lends itself to more extensive cross-linking. The latter produced a polymer with higher Tg (e.g. about 76 °C). This cross-linking reactivity generally decreases as the molecular weight of the polymer increases and as the linker chain length increases sufficiently, e.g. dodecanedioic acid (e.g. about 53°C). Similar data are provided in Table 3c, which show that different aromatic linkers of different structural rigidity resulted in different Tg values. All these data show that the transition temperature Tg not only varies with the number of carbons of a straight aliphatic chain linker but also might vary based on other properties of the linker molecule such as, but not limited to, hydrophobicity, structural rigidity, heteroatoms present, etc. It is evidenced by the results shown in Tables 3a, 3b, and 3c that the polymers of this patent evidence an extraordinary range of properties that may be varied as required by any one specific application.

These data also show that poly-NSAIDs may be created from combinations of monomers containing different linker chain lengths, with physical properties in between those of the respective homologous polymers. For example, a co-polymer made from equal amounts of monomers prepared with 6 and 8 carbon atoms had intermediate T_g and tensile modulus values. This flexibility applies to both polySA and polyDF, allowing control of polymer properties by varying the monomer ratio, e.g. 20:80, 50:50, 80:20, etc.

Table 3a: Effect of Linker Chain Length on Tensile Modulus

Linker Carbon #	6	6:8	8	10
T_g (°C)	44	38	29	16
Tensile Modulus (kPa)	3300 (25°C) 480 (37°C)	2100 (25°C) 45 (37°C)	140 (25°C) 4 (37°C)	7 (25°C) -

Varying the linker chain length also influences polymer hardness as well. In this case the relative hardness of polymers of the invention, e.g. polySA and polyDF, when measured by ASTM methods, decreased as the linker chain length increased, and the polymers became slightly softer when hydrated. Normalizing the data to the intended use temperature ($T-T_g$) showed a roughly linear relationship for all polymers, thereby creating a convenient application design tool. See, Figure 8. Essentially across this range, polyNSAIDs were highly flexible at room temperature and body temperature, as flexible as could be measured by standard ASTM methods. Soaking the polymers for an hour in 37°C PBS caused no observable change in flexibility. This is shown in Figure 7.

In another experimental design with polyanhydride esters made with either aromatic and aliphatic linkers of varying length and chemical structure, the results shown in Tables 3b and 3c shown below were obtained.

Table 3b: Poly(Anhydride-Esters) with Aliphatic Linker

Polymers[b]	**MW**	**PDI**	**T_g** (°C)	**T_m** (°C)	**T_d** (°C)
Glutaric (1a)	3,206	1.1	58	175	424
Adipic (1b)	2,221	1.7	76	*a*	391
Dodecanedyol (1c)	18,427	1.8	53	178	434

Diglycolyl (1d)	3,051	1.0	68	*a*	408

[a]. Not observed
[b]. Synthesized at 180°C for 2.5 hrs under vacuum

Table 3c: Poly(Anhydride-Esters) with Aromatic Linker

Polymers[b]	MW	PDI	T_g (°C)	T_m (°C)	T_d (°C)
Terephthalic (1e)	2,101	1.3	111	*a*	436
1-4'- Phenyldiacetic (1f)	1,584	1.0	89	*a*	386
4-4'-Biphelyldicarboxy (1g)	5,531	1.1	150	*a*	463
4-4'-Oxybiscarbonyl (1h)	9,064	1.1	103	*a*	387
4-4'-(Hexafluoro isoporpylidene) dicarbonyl (1i)	9,436	1.2	149	315	464

[a] Not observed
[b]. Synthesized at 180°C for 2.5 hr under vacuum

Thus, different embodiments may be prepared changing the chemical structure of the linket that will evidence a direct or reverse correlation with the Tg of the specific type of polymers.

Polymers Used as Coatings for Medical Devices

Medical devices employed, for example as implants typically elicit foreign body responses characterized by thrombosis, inflammation, and infection, among others. Accordingly, these products increasingly are being combined with therapeutic agents to help diminish these adverse effects. Polymers of this invention such as polyNSAIDs and others having anti-inflammatory and antiseptic properties are extremely well suited for these applications. Other types of polymers described in this patent are well suited to impart properties such as biological, pharmaceutical, therapeutic or diagnostic properties.

The polymers of this patent have a broad range of fracture toughness, as measured in ksi (or 1000psi), or times the square root of an inch. Generally the fracture toughness values for the polymers of the invention fall in the range of about 0.2, 0.4, 0.5 ksi to about 0.6, 0.8, 0.9, 1.0, 1.2 ksi. Higher and lower ksi values, however are also attainable. The polymers of the invention are suitable for releasing the contained agent(s) for a broad period of time, including but not limited to 1-2 hours, 12 hrs, 24hrs, 2 days, 8 days, 2 weeks, 4 weeks, 3 months, 6 months to about 8 months, 12 months, 15 months, 18 months, 2 years, and even longer periods of time in specific applications that are specifically tailored for such purpose.

Polymer Adhesion to Metal and Non-Metal Surfaces

The metallic components of many implantable orthopedic devices are made of various alloys, such as those of nickel-titanium and cobalt-chromium. The adhesion load displacement profile of polymers in accordance to this invention, e.g. polyDF, on these metals at ambient temperature, were measured by testing polymers that were melt-coated directly onto clean, dry metal butt-joints in an Instron™ apparatus (considered an extreme test for polymer adhesion) is shown in Figure 9. On one type of satin-finish titanium alloy, polyDF exhibited a load failure of 2,030 PSI. Testing of the polymer on a cobalt-chromium alloy was interrupted at 1,630 PSI when the metal grip pins used to hold the meal test cylinder broke. These results demonstrate that polyDF adheres to these metals as tightly as commonly used epoxies and glues. ASTM test methods were used to demonstrate the strong adhesion of polymers of the invention such as polySA and polyDF to electro-polished 316L stainless steel, i.e., the metal used for coronary vascular stents. This property is in sharp contrast to other polymers, many of which adhere to metals only after special treatment of the metal surfaces.

In general the polymers of the invention exhibit excellent adhesion to non-metallic surfaces, including polymers such as biopolymers, polyanhydrides and other biocompatible and non-biocompatible polymers, mickel alloys, PMMA based materials, and the like. The polymers of this patent may be employed in conjunction and for vcovering and adhering to any material suitable for use in the applications mentioned here. The polymers of this invention achieve a broad range of cohesive failure values as measured by a 1.1" Butt Weld test. Generally, cohesive values of about 100, 200, 300, 400, 600, 700, 1000 to about 1500, 2000, 2500, 3000 psi are easily attained. The lower value represents minimal adhesion whereas the higher value represents cohesive failure of the polymer. Much broader range values are consistently achieved on surfaces such as titanium alloys, stainless steel, cobalt alloys, and chromium alloys.

Polymer Biodegradation

The degradation of polymers according to the invention, such as polySA and polyDF, was tested with polymers coated onto samples of electro-polished 316L stainless steel. The polymers were dissolved in anhydrous chloroform and spread into thin films onto dry metal surfaces that had been cleaned with acetone, after which the solvent was removed overnight in a 40°C vacuum oven. A 5 μm layer of polySA incubated in pH 7.4 PBS at 37°C generated salicylic acid for about one week as shown in Figure 10. While not apparent from the figure, it should be noted that polySA did not begin to degrade until 8-10 hours after exposure to buffer or serum. This "induction period" is characteristic of poly(anhydride-ester) polymers; in general, the higher the molecular weight, the longer the induction time. In contrast, a similar 5 μm layer of polyDF generated diflunisal for over two months. Kinetic analysis of these data (Figure 11) indicate that the generation of salicylic acid from polySA proceeded in a sharply bi-phasic, non-linear rate, while the generation of diflunisal from polyDF was mono-phasic and linear. This high molecular-weight polymer has an induction time of 15-18 hours. These different kinetic profiles may be partly explained by the different degradation mechanisms of polySA versus polyDF. So-called "bulk eroding" polymers degrade throughout their structure, like a limp of sugar in water. Because essentially the whole polymer mass is available for degradation, the greater the amount of a bulk eroding polymer, the more breakdown product generated over time. This is exactly the case with polySA; when solid disks of this polymer were incubated in 37°C PBS, the thicker disks generated more salicylic acid. See, Figure 12.

"Surface-eroding" polymers, on the other hand, degrade only from their surface, like a bar of soap. Since only the polymer surface is available for degradation, the generation or breakdown products over time generally does not vary with polymer mass. This is the case with polyDF; when disks of this polymer were incubated in 37°C PBS, the same amount of diflunisal was generated regardless of disk thickness (Figure 13). The surface eroding property of polyDF makes it ideal for use as coatings in settings where a constant, controlled rate of drug delivery is desired. This property of polyDF enabled an evaluation of the effect of polymer molecular weight on the generation of diflunisal. Two preparations of polyDF (molecular weights 33K and 100K) produced by the melt-condensation method were solvent coated onto electro-polished stainless steel samples and incubated in 37°C serum, which contains esterase enzymes that might be expected to contribute to polymer degradation in the body. As shown in Figure 14, the 33K polymer degraded much more rapidly than the 100K polymer, which as in PBS generated diflunisal for about two months. The molecular profile of the products of polymer degradation that may be generated over a period of time is another important characteristic of biodegradable polymers. Polymers that biodegrade consistently into a small number of breakdown products are generally have good biocompatibility, and will encounter fewer regulatory hurdles. An HPLC profile of the soluble breakdown products generated during polymer degradation, e.g. the degradation of polySA in 37°C serum is shown in Figure 15. In the case of polySA, the HPLC chromatograms showed only breakdown products that contain salicylic acid with the linker itself not being observed. After two days, the main breakdown product in serum was salicylic acid, which exhibited a 2-minute elution time. Also observed were minor amounts of the monomer and several oligomers. By day three, the elution profile indicated increasing amounts of salicylic acid, with smaller amounts of monomer and oligomers. After seven days, only salicylic acid and one other compound were apparent, and by day 13, only salicylic acid was observed. The pattern of soluble breakdown products generated during the degradation of polyDF in 37°C serum was less complex. consisting of diflunisal itself with a 7-minute elution time, with no other breakdown products observed in serum up to two days, and at every point thereafter. See, Figure 16.

<u>Biodegradation of Polymers Containing Admixed Drugs</u>

For many medical device applications it may be desirable to use polymers in accordance with this invention, e.g. polyNSAIDs, in combination with other drugs added to the polymers to produce additional therapeutic effects. Such "solid solution" preparations may be created by simply mixing a polymer dissolved in a solvent with a solution of another drug dissolved in the same solvent, or by any other method known in the art. Evaporation of the solvent results in a homogeneous solid solution of drug in polymer. The usefulness of the invention's polymers in medical devices, such as drug-eluting coronary stents and others, led the inventors to prepare and evaluate solid solutions of, for example polyDF containing 20wt% paclitaxel or sirolimus \, i.e. 1 mg of polymer/drug admixture contained 0.8 mg polymer and 0.2 mg drug). Figure 17 shows the concurrent release of paclitaxel from a polyDF/paclitaxel admixture coated onto electropolished stainless steel samples and incubated in 37°C serum. Paclitaxel was released at the same rate at which the polymer biodegraded to generate diflunisal (the relatively small percentage of paclitaxel released reflects the inability of serum to hold this very poorly water-soluble drug). The incorporation of paclitaxel into the polymer did not affect the generation of diflunisal, which proceeded at the same rate as from polyDF without paclitaxel. Similar results were obtained with a polyDF/sirolimus admixture.

Effects of Sterilization by Various Methods

All implantable and percutaneous medical devices must be sterilized before or after packaging. Sterilization methods commonly employed are gamma irradiation, electron beam ("E-beam"), and ethylene oxide. Sterilization by gamma radiation penetrates objects deeply, and is used for food and many medical device products, but the method requires relatively prolonged exposure times. E-beam sterilization allows shorter exposure times, but the electrons penetrate objects poorly, making the procedure useful mainly for surfaces. Ethylene oxide sterilization is more complex and more aggressive on organic materials than the other methods and is being replaced where possible due to environmental hazards. The relatively high temperatures and humidity employed in many ethylene oxide sterilization protocols is not very compatible with poly(anhydride-ester) polymers. Accordingly, gamma radiation and E-beam sterilization methods are preferred for use with such compositions. Figure 18 shows that the sterilization with E-beam (3.5 mRad) and gamma radiation (25-35 Kgys) had no effect on the pattern of diflunisal generated from polyDF coated stainless steel samples incubated in 37°C serum. Notwithstanding the lack of effect on polymer degradation, sterilization does produce some changes in molecular weight and mechanical properties. For example, the tensile modulus of melt-polymerized polySA at room temperature decreased by about a third after gamma sterilization (25-35 Kgys), but there was no change at 37°C. Gamma radiation had no effect on the molecular weight, flexibility, or adhesiveness of the polymers of the invention, such as polySA and poly DF, and only minor effects on hardness.

POLYMER MICROPARTICLES FOR PHARMACEUTICAL PRODUCTS

All of the foregoing pharmaceutical applications may employ microparticular formulations. Figure 19, for example, shows microspheres made form polyDF that have a mean diameter of about 45μm, slightly smaller than the size commonly used for drug delivery. The surface eroding property of polymers such as polyDF makes solid, non-porous microparticles, e.g. microspheres, useful for sustained drug delivery, and their release duration may be controllable by varying the particle diameter, e.g. larger microparticles biodegrade more slowly than smaller ones. Microparticles for pharmaceutical products may be designed to deliver the drug incorporated into the polymer backbone. In one study rats were administered a single subcutaneous injection of 250 mg polyDF microspheres containing about 192 mg diflunisal by weight, formulated in a standard aqueous vehicle. Figure 20 shows that a peak plasma diflunisal levels of about 35 μg/ml was achieved within two days, after which drug levels declined slowly over about two weeks in contrast to a single oral dose of diflunisal, the levels of which declined rapidly. Similarly, nanoparticle formulations may be administered for various applications, having a particle size about 1, 2, 5, 10 to about 15, 20, 30, 50, 100, 250, 500 nm, or various ranges between any two of these values. These polymers may also be employed as carriers for other drugs, as has been demonstrated with paclitaxel and sirolimus. The anti-inflammatory property of PolyNSAIDs as a delivery vehicle for admixed drugs and biologicals is expected to significantly diminish the foreign body response associated with polymers commonly used for injectable depot products, such as PLGA. While the injection of a drug or biological agent in a polymer of this invention, e.g. a polyNSAID, carrier may be expected to generate significant drug, e.g. NSAID, concentrations in tissues near the injection site, their systemic levels in most cases will remain <0.1μ, which are far below therapeutic levels.

Polymer Coatings for Stents and Grafts

The example provided by the remarkable effectiveness of drug-coated stents in reducing the incidence of coronary arterial restenosis represents at the same time a breakthrough in the treatment of vascular disease, and provides a model for other applications of the present invention. Most leading stents under development are based on the sustained delivery of anti-proliferative and/or immunosuppressive drugs like paclitaxel and sirolimus. These drugs were selected because of their ability to reduce the over-growth of smooth muscle cells that occurs after insertion of stents into the arterial wall. Other drugs, such as dexamethasone, however, are being tested because of their ability to reduce inflammation, and many others may be employed as illustrated by Figure 21. Stents are inserted, and then over-expanded into the arterial wall so that they will remain lodged in place. This produces a "wound" that rapidly leads to fibrin clot formation that walls off the damaged area, a process called thrombus deposition. At the same time inflammation induces immune system cells to migrate into the area in order to engulf and destroy damaged cells in a classic response to a foreign body. This causes smooth muscle cells to overproliferate in the damaged area, and leads to abnormal tissue remodeling, also called restenosis. While the use of anti-proliferative drugs is a rational strategy to reduce restenosis, the overproliferation of arterial smooth muscle cells is thought to be a direct consequence of inflammation. The sustained delivery of drugs as disclosed in this patent, e.g. anti-inflammatory and other drugs, into the damaged area does itself prevent or substantially reduce the development of restenosis. The inventors have produced coronary stents coated with polymers such as polyNSAIDs, and sterilized them for animal testing. Figure 22 shows these stents immediately after coating with 1mg polySA (5μm thickness), after E-beam sterilization, after expansion via a balloon catheter, and after soaking in 37°C serum for two hours. Similar results were obtained with polyDF. Polymer-coated stents, such as polyNSAID-coated stents, were implanted into the iliac arteries of rabbits employing uncoated stents as controls. Figure 23 shows histological arterial sections collected seven days post-implantation of polySA-coated stents revealing no evidence of thrombosis or inflammation when compared to controls. Although the polymer coating is not apparent in these sections during in vitro testing polySA bulk-erodes within about 1 week. Rabbit iliac arterial sections collected 7 days after implantation of polyDF-coated stents again revealed no thrombosis or inflammation as seen in Figure 24. In contrast to the results obtained with polySA, these arterial sections clearly reveal the presence of the polyDF coating. In vitro tests evidenced that the latter will last at least 1 month. The effect of polySA-coated stents were evaluated as well at 28 days post implantation, and were found to be indistinguishable from uncoated controls most likely due to prior polymer depletion. Arterial sections from polyDF-coated stents revealed that the polymer was still present after 28 days, but evidenced only very mild inflammation (figure not shown).

In a follow-on study, pig coronary arteries were implanted with stents coated with 1mg polyDF alone, with polyDF containing 200μg paclitaxel and with polyDF containing 200 μg sirolimus. After 28 days the arteries receiving stents coated with polyDF alone showed considerably less fibrin deposition, hemorrhage, and inflammation than those treated with polyDF plus sirolimus or paclitaxel. These results are applicable also to polyNSAID coatings for self-expanding nitinol stents and grafts for non-coronary applications, e.g. endovascular applications, and are in marked contrast to the non-degradable, inflammation-generating polymers currently used for drug-coated stents. Results from 28-day and 90-day pig studies demonstrate that polyNSAIDs are the first biocompatible, biodegradable, anti-inflammatory materials effective for coronary stents, and to deliver drugs of interest. Some characteristics of polyNSAIDs and prior art polymer coatings currently used on drug-eluting stents are provided in Table 4 below.

Table 4: PolyNSAIDs vs. Current Polymer Stent Coatings

PolyNSAID Coatings	Current Polymer Coatings
Biodegradable	Non-biodegradable
Pharmacologically active	Pharmacologically inactive
Little/no inflammation	Significant inflammation
Additional drug OK	Additional drug not OK
Easily applied to metals	Application complex

The ability of the polymers of this invention, e.g. polyNSAIDs, to adhere strongly to metal, e.g. stainless steel, without need for glues or other surface treatments provides an important advantage over other available stents, and eliminates the need for treating the metal surface prior to affixing a drug-eluting polymer, and/or for an additional layer with another polymer coating to prolong drug release and prevent a "burst effect".

Polymer Coatings for Implanted Orthopedic Joint-Replacement/ Aid Devices

Joint-replacement implants and bone aid devices are widely used to restore quality of life for million of patients with irreparably damaged shoulders, knees, and hips as well as for repairing broken and splintered bones. These devices are generally made of titanium/nickel or cobalt/chromium alloys, with metal stems that are inserted into the hollow portion of the arm or leg bones. Some of these stems have smooth surfaces that require the use of bone cement to ensure strong connection, while others have highly engineered, honeycomb-textured surfaces that become partially filled with bone and marrow cells during insertion, thereby seeding the stem for in growth of new bone and reducing the need for cement. Orthopedic surgeons are eager to incorporate agents into these surfaces that may accelerate bond growth. A number of recombinant bone morphogenic proteins (BMPs) and other "osteogenic" proteins are in development for this purpose, notwithstanding their high manufacturing costs and product development challenges. The dynamics of bone formation, resorption, and repair are complex, and appear to vary for different types of bone. Dental studies showed that the inhibition of prostaglandin production by NSAIDs decreases bone resorption in the trabecular bone of the palate and alveolar bone of the jaw, causing a net increase in bond mass and density. This phenomenon was demonstrated in the mouse for "PolyAspirin" implants). In addition, polySA prevented bone erosion in a rat femur transaction model. Other animal studies suggest that the repair of long-bone fractures may be inhibited by long-term exposure to high levels of NSAIDs. Different forms of the present polymers may be prepared that are suitable for these and other applications in the orthopedics and dental fields, among others. Polymers of this invention, such as polyNSAIDs and others, may be employed as coatings to reduce pain and inflammation associated with device implantation and adjustment of dental and orthopedic aids, to reduce the incidence of infection, which is a major problem associated with joint replacement devices, and to prevent and treat other conditions by delivering appropriate agents to the site. While infection at the implant/bone interface reportedly occurs in less than 1% of cases, the limited blood supply to the region makes these infections particularly hard to treat with systemic antibiotics. The antiseptic properties of a polymer of the invention, such as a polyNSAID, a polyantibiotic, a combination or mixture thereof, in a coating prevents or greatly reduces infection without the potential for bacterial resistance. Together with the properties of polymers such as polyNSAIDs summarized in Table 4, this characteristic makes PolyNSAIDs attractive for use on orthopedic, dental, ocular, and many other implanted medical devices.

Injectable Polymers SR™ for Auto-Immune Disease

Immune diseases such as rheumatoid arthritis (RA), lupus, and the like, are debilitating diseases affecting millions. RA will be discussed as a representative condition of this group. By far the most troubling symptoms of RA are severe pain and swelling of the joints of the wrists, hands, ankles and feet, which occur when the body's immune system mistakenly attacks the synovium (the cells lining the joints), causing intense inflammation. The therapeutic mainstay of RA is oral NSAIDs, including non-selective COX inhibitors like aspirin and diflunisal, as well as the newer COX 2-specific NSAIDs, rofecoxib and celecoxcib. As disease severity progresses, disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate, azothioprine, gold salts and immunosuppressive agents are used, despite their serious side effects. More recently, injectable biological response modifiers that block the action of tumor necrosis factor (etanercept and infliximab) have shown great promise, despite their high cost and associated risk of tuberculosis and cancer. Another injectable protein (anakinra) blocks the effects of IL-1, an inflammatory protein over-expressed in RA patients. Notwithstanding the effectiveness of these newer treatments, RA remains a chronic disease, the severity of which fluctuates over time. When pain and swelling flare, a standard treatment is to inject steroids directly into the affected joint, sometimes in combination with a local anesthetic. Such intra-articular injections provide rapid and long-lasting relief of pain and swelling, but only a few steroid injections may be administered safely at any one time, and repeated injections into the same joint may destroy cartilage. These drawbacks have spurred the development of "steroid-sparing" treatments for flared joints. A PLGA microsphere-based intra-articular product is being currently tested to provide slow-release of betamethasone, with the goal of minimizing tissue damage whereas intra-articular hyaluronic acid products are used mostly for osteoarthritis.

In one embodiment, the present invention is an injectable polymer, e.g. a polyNSAID product, comprising microparticles designed to provide sustained relief of swollen and painful joints after intra-articular injection and other uses. On eexample is a microformulation of polyDF. In cases where polyDF alone may be insufficient, other drugs, including analgesics such as morphine, may be added during during preparation of the microparticle formulation, or as a coating or core of the formulation. Long considered to produce analgesia by the activation of receptors located only within the central nervous system, new evidence demonstrates that narcotic analgesics have a potent local analgesic effect when injected into chronically-inflamed tissue. Cinical studies demonstrated profound pain relief from 1mg morphine injected into chronically-inflamed (but not acutely-inflamed) gum tissue, and pain relief similar to that of 4 mg dexamethasone by the intra-articular injection of 3 mg morphine in RA patients.

The addition of strong analgesics, such as narcotic analgesics, e.g. morphine, to the polymer of the invention presents little or no abuse potential because only low concentrations of morphine are required, generally less than about 5 to 10wt% as is known in the art, and morphine release from polyDF will be retarded generally by an about 15- to about 18-hr induction period before the onset of polymer biodegradation. For more extended effects, e.g. analgesia, antibiotic and antiseptic action, and the like, drugs such as narcotic analgesics, antibiotics, and other drugs, may also be incorporated into the backbone of the polymer.

Polymer Microparticle Formulations for Injectable Biological Products

More than 20 companies worldwide are working with polymer-based depot products. The major marketed products in this area are LUPRON DEPOT® (leuprolide for prostate cancer and endometriosis), NUTROPIN DEPOT® (human growth hormone), TRELSTAR DEPOT® (triptorelin for prostate cancer), and SANDOSTATIN LAR® (octreotide for acromegaly). These products generated combined sales of over $2.5 billion in 2001. More generally, the sale of drug delivered products is projected to increase to $42 billion by 2007, at an annual growth rate of about 12%. Key drivers for this growth are expected to be branded drug and biological products requiring product line extension, and new drug and biological products requiring delivery systems that improve patient compliance. Several leading products are summarized in Table 5 below.

Table 5: Injectable Drug and Biological Depot Products

COMPANY	PRODUCT	DRUG	FORMULATION
Chiron	DEPOCYTE®	Cytarabine	Depofoam™ liposome)
SkyePharma	DepoMorphine™	Morphine	Depofoam™ liposome)*
TAP Pharma	LUPRON DEPOT®	Leuprolide	Medisorb™ (PLGA)
Genentech	NUTROPIN DEPOT®	HGH	Medisorb™ (PLGA)
Pharmacia	TRELSTAR DEPOT®	Triptorelin	Medisorb™ (PLGA)
Novartis	SANDOSTATIN LAR®	Octreotide	PLGA
J & J	Risperdal Consta™	Resperidone	Medisorb™ (PLGA)*

*** Currently in Development**

Many new products contain proteins formulated with aqueous suspensions of PGLA microspheres. While generally considered to have acceptable biodegradation kinetics, safety and biocompatibility, PLGA elicits localized inflammation and foreign body response, which may be severe depending on the tissues involved. This is evidenced by clinical studies involving 138 pediatric patients who received subcutaneous injections of NUTROPIN DEPOT®, a recombinant human growth hormone formulated with PLGA microspheres. Almost every patient reported two or three "injection site reactions" per injection, most of which represent hallmark foreign-body reactions, as shown in Table 6 below whereas patients receiving aqueous formulations of NUTROPIN reported infrequent foreign-body reactions. The inventors believe polymers of this invention, such as polyNSAID microparticles, provide safe injectable depot formulations for proteins, monoclonal antibodies, polysaccharide, and nucleic acid prophilactic and therapeutic products with improved tolerability, enhanced bioavailability, and lower production costs compared to PLGA-based products.

Table 6: Reported Injection Site Reaction with NUTROPIN Products

NUTROPIN DEPOT®	INCIDENCE
granuloma (nodules)	61%
erythema (redness)	53%
pain after injection	47%

pain during injection	**43%**
bruising	**20%**
itching	**13%**
swelling/puffiness	**8%**
NUTROPIN AQ®	
injection site – discomfort	**"has been reported"**
NUTROPIN®	
injection site plan	**"reported infrequently"**

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All publications, patents, and patent application documents are incorporated by reference herein in their entirety, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.